(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 November 2004 (04.11.2004)

PCT

(10) International Publication Number
WO 2004/094671 A2

(51) International Patent Classification[7]: C12Q 1/68

(21) International Application Number: PCT/US2004/012788

(22) International Filing Date: 22 April 2004 (22.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/464,586	22 April 2003 (22.04.2003)	US
60/464,588	22 April 2003 (22.04.2003)	US

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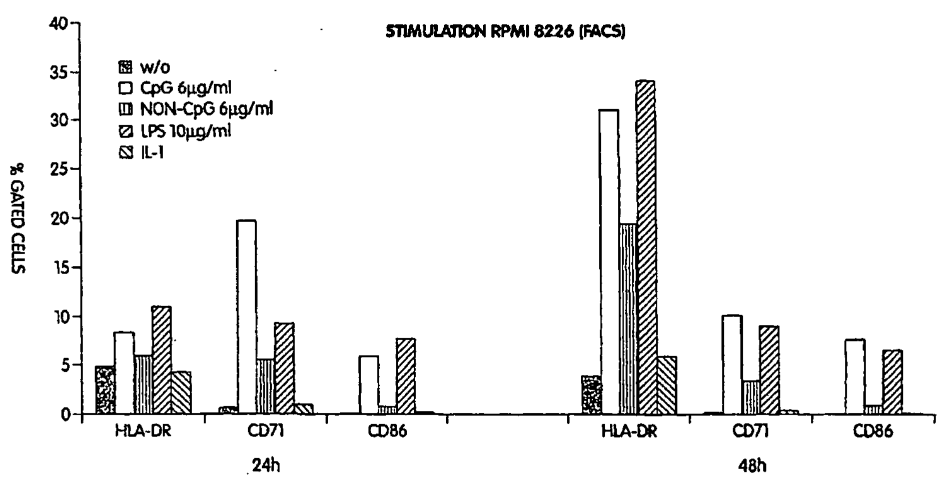
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: METHODS AND PRODUCTS FOR IDENTIFICATION AND ASSESSMENT OF TLR LIGANDS



(57) Abstract: The invention provides in part novel screening methods and compositions for identifying and distinguishing between candidate immunomodulatory compounds. The invention further provides methods for assessing biological activity of composition containing a known TLR ligand. These latter methods can be used for quality assessment and selection of various lots of test compositions, including pharmaceutical products for clinical use.

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GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS AND PRODUCTS FOR IDENTIFICATION AND ASSESSMENT OF TLR LIGANDS

Background of the Invention

Nucleic acids with immunostimulatory activity have been identified. The first recognized immunostimulatory motif was the CpG motif in which at least the C of the dinucleotide was unmethylated. It has been postulated that mammalian subjects recognize the unmethylated dinucleotide as being of bacterial origin, and thus mount a heightened immune response following exposure. The ensuing immune response includes both cell mediated and humoral aspects. Since the discovery of the CpG immunostimulatory motif, other immunostimulatory motifs have also been identified including the poly-T and T-rich motifs, the TG motif and the poly-G motif. In some instances, immunostimulation has also been observed in response to exposure to methylated CpG motifs and motif-less nucleic acids having phosphorothioate backbone linkages.

The responses induced by immunostimulatory nucleic acids are varied and can include production and secretion of cytokines, chemokines, and other growth factors. The nucleic acids can induce a heightened immune stimulation regardless of whether an antigen is also introduced to the subject. Identification of new motifs as well as of subtle differences between response profiles of different nucleic acids oftentimes can be laborious, and a high throughput system for screening nucleic acids for their ability to be immunostimulatory as well as to determine the profile of responses they induce would be useful.

Summary of the Invention

The invention provides in its broadest sense screening methods and tools for identification and discrimination of immunomodulatory molecules and assessment and standardization of samples containing known immunomodulatory molecules. The immunomodulatory molecules can be immunostimulatory or immunoinhibitory, and most preferably are Toll-like receptor (TLR) ligands.

In one aspect, the invention provides a screening method for identifying TLR agonists. The method comprises contacting a cell line endogenously expressing at least one TLR with a test compound and measuring a test level of TLR signaling activity, wherein a positive test level is indicative of a TLR agonist (i.e., an immunostimulatory compound). The positive test

level may be apparent without referring to a control. Preferably, however, it is determined relative to a control (i.e., the TLR signaling activity from a reference compound).

In some embodiments, the reference compound is a compound that induces no response (i.e., a zero response) or a minimal response. In this case, a test level that is greater than the reference level is indicative of a compound with TLR signaling activity. More preferably, the reference compound is a compound that induces a positive response (i.e., a non-zero response) and that is immunostimulatory. These reference compounds are referred to herein as negative and positive reference compounds, respectively. If the reference compound is immunostimulatory (i.e., a positive reference compound), a non-zero test level that is lower than the reference level is still indicative of an immunostimulatory test compound. In this latter embodiment, the test compound is less immunostimulatory than the reference compound (for that particular readout), but it is nonetheless immunostimulatory given the non-zero response induced. There may be one or more concurrent or consecutive assays with a negative reference compound, a positive reference compound, or both. The reference may also be a standard curve or data generated previously.

In a related aspect, the screening method involves exposing the same cell to a positive reference compound and a test compound in order to identify a test compound that inhibits the immunostimulatory response of the positive reference compound (i.e., a TLR antagonist or an immunoinhibitory compound).

In still a related aspect, the screening method involves exposing the same cells to a positive reference compound and a test compound in order to identify a test compound that enhances the immunostimulatory response of the positive reference compound (i.e., an enhancer).

In both of these latter aspects, the assay requires a co-incubation of the positive reference compound, the test compound and the cells. Separate assays with positive reference compound alone and optionally negative reference compound alone are usually also performed.

The positive reference compound is a known TLR ligand. Non-limiting examples include but are not limited to TLR3 ligands, TLR7 ligands, TLR8 ligands and TLR9 ligands. In some embodiments, the positive reference compound is an immunostimulatory nucleic acid. In some embodiments, the positive reference compound is a CpG nucleic acid, a poly-T nucleic acid, a T-rich nucleic acid or a poly-G nucleic acid. Another example of a positive

reference compound is a nucleic acid comprising a backbone that contains at least one phosphorothioate linkage.

It has been further discovered according to the invention that the RPMI 8226 cell line expresses TLR7 and responds to the imidazoquinoline compound R-848 (Resiquimod) which is known to signal through TLR7 and TLR8. Accordingly, the screening method can be performed using RPMI 8226, Raji or RAMOS cells and an imidazoquinoline compound such as R-848 or R-847 (Imiquimod) as the positive reference compound.

In one embodiment, the test compound is a nucleic acid such as but not limited to a DNA, an RNA and a DNA/RNA hybrid. The test compound may be a nucleic acid that does not comprise motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif. The test compound may be a nucleic acid that comprises a phosphorothioate backbone linkage. In another embodiment, the test compound is a non-nucleic acid small molecule. The non-nucleic acid small molecule may be derived from a molecular library. In other embodiments, the test compound comprises amino acids, carbohydrates such as polysaccharides. It may be a hormone or a lipid or contain moieties derived therefrom. In other embodiments, the test compounds are putative ligands for TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10 or TLR11.

In one embodiment, the cell is a RPMI 8226 cell, a Raji cell, a RAMOS cell, a THP-1 cells, a Nalm cell or a KG-1 cell and the TLR is TLR9. In another embodiment, the cell is a RPMI 8226 cell, a Raji cell or a RAMOS cell and the TLR is TLR7. In yet another embodiment, the cell is a KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a Hela cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell and the TLR is TLR3.

In another embodiment, the cell is an RPMI 8226 cell and the TLR is TLR7 or TLR9. In still another embodiment, the cell is a Raji cell and the TLR is TLR9, TLR7 or TLR3.

Depending upon the embodiment, the TLR signaling activity may be measured or detected in a number of ways. In one embodiment, the TLR signaling activity is measured by cytokine, chemokine, or growth factor secretion. The cytokine secretion may be selected from the group consisting of IL-6 secretion, IL-10 secretion, IL-12 secretion, IFN-α secretion and TNF-α secretion, but is not so limited. The chemokine secretion may be IP-10 secretion or IL-8 secretion, but is not so limited.

In another embodiment, the TLR signaling activity is measured by antibody secretion. The antibody secretion may be IgM secretion, but is not limited to this antibody subtype.

In another embodiment, the TLR signaling activity is measured by phosphorylation. The total level of phosphorylation in the cell or the level of phosphorylation of particular factors in the cell may be measured. These factors are preferably signaling factors and can be selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, Jun, c-fos, and subunits of NF-κB, but are not so limited.

In still a further embodiment, the TLR signaling activity is measured by cell surface marker expression. In one embodiment, the TLR signaling activity is measured by an increase in cell surface marker expression. Examples of cell surface markers to be analyzed include CD71, CD86, HLA-DR, CD80, HLA Class I, CD54 and CD69. In other embodiments, the TLR signaling activity is measured by a decrease in cell surface marker expression. Cell surface marker expression can be determined using flow cytometry. TLR signaling activity can also be measured by protein production (e.g., by Western blot).

In another embodiment, the TLR signaling activity is measured by gene expression. Gene expression profiles may be determined using Northern blot analysis or RT-PCR that uses mRNA or total RNA as a starting material. The gene expression of interest may be that of the chemokines and cytokines and cell surface molecules recited above. Gene expression analysis can be performed using microarray techniques.

In yet another embodiment, the TLR signaling activity is measured by cell proliferation. Cell proliferation assays can be measured in a number of ways including but not limited to ^{3}H-thymidine incorporation.

In one embodiment, the cell is an RPMI 8226 cell and TLR signaling is indicated by expression of a marker such as CD71, CD86 and/or HLA-DR or by expression, production or secretion of a factor such as IL-8, IL-10, IP-10 and/or TNF-α. Preferably, in this latter embodiment, the RPMI 8226 cell is unmodified. In another embodiment, the cell is a Raji cell and the TLR signaling is indicated by IL-6 or IFN-α2 expression, production or secretion. In yet another embodiment, the cell is a RAMOS cell and the TLR signaling is indicated by CD80 cell surface expression.

TLR signaling activity can be measured via a native readout or an artificial readout or both. A native readout is one that does not rely on introduction of a reporter construct into the cell of interest.

The cell line may be used in a modified or unmodified form. In one embodiment, the cell line is transfected with a reporter construct. The transfection may be transient or stable. The reporter construct generally comprises a promoter, a coding sequence and a

polyadenylation signal. The coding sequence may comprise a reporter sequence selected from the group consisting of an enzyme (e.g., luciferase, alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase (CAT), secreted alkaline phosphatase, etc.), a bioluminescence marker (e.g., green fluorescent protein (GFP, U.S. Patent No. 5,491,084), etc.), a surface-expressed molecule (e.g., CD25), a secreted molecule (e.g., IL-8, IL-12 p40, TNF-α, etc.), and other detectable protein sequences known to those of skill in the art. Preferably, the coding sequence encodes a protein, the level or activity of which can be quantified, with preferably a wide linear range.

In some embodiments, the promoter is a promoter that is responsive to TLR signaling pathways (i.e., a "TLR responsive promoter"). In some embodiments, the promoter contains a binding site for a transcription factor activated upon CpG nucleic acid exposure, such as for example NF-κB. In other embodiments, the promoter contains a binding site for a transcription factor that is activated by a positive reference compound other than CpG nucleic acids. The transcription factor binding site may be selected from the group consisting of a NF-κB binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE, as well as others known to those of skill in the art.

In another embodiment, the promoter contains a functional promoter element from an IL-1 gene, an IL-6 gene, an IL-8 gene, an IL-10 gene, an IL-12 p40 gene, an IFN-α1 gene, an IFN-α4 gene, an IFN-β gene, an IFN-γ gene, a TNF-α gene, a TNF-β gene, an IP-9 gene, an IP-10 gene, a RANTES gene, an ITAC gene, a MCP-1 gene, an IGFBP4 gene, a CD54 gene, a CD69 gene, a CD71 gene, a CD80 gene, a CD86 gene, a HLA-DR gene, and a HLA class I gene.

The TLR responsive promoter may be a TLR1 responsive promoter, a TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter, a TLR10 responsive promoter or a TLR11 responsive promoter.

In these latter embodiments, the cell line may be transfected with a reporter construct having a promoter derived from a particular cytokine, chemokine, or cell surface marker, and a unique reporter coding sequence conjugated thereto. In this way, the readout from a particular reporter construct is a surrogate readout for cytokine, chemokine, or cell surface marker readout. Measuring readout from the reporter coding sequences described herein is in

some instances easier than measuring cytokine or chemokine secretion, or upregulation of a cell surface marker.

In these latter embodiments, the cell line may be transfected with a number of reporter constructs each having a promoter derived from a particular cytokine, chemokine, or cell surface marker, and a unique distinguishable coding sequence conjugated thereto. In these embodiments, multiple readouts are possible from one screen. In other embodiments, multiple native readouts are also possible from one screen.

In a related embodiment, the cell may be further transfected with a nucleic acid that codes for a TLR polypeptide or a fragment thereof. Preferably, the TLR is one that is not endogenously expressed by the cell. As an example, if the cell is an RPMI 8226 cell which has been shown to express TLR7 and TLR9 according to the invention, then it may be modified to express TLRs other than these (e.g., TLR8) in some embodiments. In this aspect, the RPMI 8226 cell is responsive to TLR8 ligands. In preferred embodiments, the TLR is a human TLR (i.e., hTLR).

In another aspect, the invention provides an RPMI 8226 cell transfected with a TLR nucleic acid. In still another embodiment, the TLR nucleic acid is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR8, TLR10 and TLR11. The encoded TLRs nucleic acids can derive from human or non-human sources. Examples of non-human sources include, but are not limited to, murine, bovine, canine, feline, ovine, porcine, and equine species. Other species include chicken and fish, e.g., aquaculture species. The TLR nucleic acids can also include chimeric sequences consisting of domains originating from different species. In preferred embodiments, the TLR is a human TLR.

In still another aspect, the invention provides kits including the cells lines (e.g., the RPMI 8226 cell line), the reporter constructs and/or expression constructs described above, and instructions for use.

Other aspects of the invention provide methods for analyzing the biological activity of individual lots of material containing previously identified specific TLR ligands (i.e., specific compounds which are ligands for a particular TLR) intended for use as, or for use in the preparation of, pharmaceutical compositions. The methods permit a qualitative and, importantly, a quantitative assessment of biological activity of individual lots of TLR ligands, pre-formulation as well as post-formulation. Such methods are useful in the manufacture and validation of pharmaceutical compositions containing, as an active agent, at least one specific ligand of at least one specific TLR. The specific TLR can be any known TLR, including

without limitation TLR3, TLR7, TLR8 and TLR9. The specific TLR ligand is an isolated TLR ligand, either found in nature or synthetic (not found in nature), including in particular certain nucleic acid molecules and small molecules. Nucleic acid molecules that are specific TLR ligands include synthetic and naturally-occurring oligonucleotides having specific base sequence motifs. Furthermore, specific TLR ligands include both agonists and antagonists of specific TLR.

These methods are to be distinguished from test procedures and acceptance criteria for new drug substances and new drug products which are classified as chemical substances. Unlike the afore-mentioned test procedures and acceptance criteria, the methods of the instant invention deal specifically with characterizing drug substances and drug products which are classified as oligonucleotides. Oligonucleotides are explicitly excluded in ICH Topic Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Step 4 – Consensus Guideline: 6 October 1999, § 1.3.

Further still, the methods of the instant invention are to be distinguished from test procedures and acceptance criteria for biotechnological/biological products. Unlike the afore-mentioned test procedures and acceptance criteria, the methods of the invention deal specifically with characterizing biotechnological/biological products which are classified as DNA products. DNA products are explicitly excluded in ICH Harmonised Tripartite Guideline Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, Step 4 – 10 March 1999, § 1.3.

In one aspect, the invention provides a method for quality assessment of a test composition containing a known TLR ligand. The method according to this aspect of the invention involves measuring a reference activity of a reference composition comprising a known TLR ligand, wherein the known TLR ligand is a nucleic acid molecule; measuring a test activity of a test composition comprising the known TLR ligand; and comparing the test activity to the reference activity. In one embodiment the method further involves the step of selecting the test composition if the test activity falls within a predetermined range of variance about the reference activity.

In one embodiment, the reference composition is a first production lot of a pharmaceutical composition comprising the known TLR ligand, and the test composition is a second production lot of a pharmaceutical composition comprising the known TLR ligand. This embodiment is particularly useful as a method for developing and applying acceptance criteria for finished pharmaceutical products containing a known TLR ligand.

In another embodiment, the reference composition is a first in-process lot of a composition comprising the known TLR ligand, and the test composition is a second in-process lot of a composition comprising the known TLR ligand. This embodiment is particularly useful as a method for developing and applying acceptance criteria for raw materials and/or other in-process materials containing a known TLR ligand bound for use in a pharmaceutical product.

In one embodiment according to this aspect of the invention, measuring the reference activity involves contacting the reference composition with an isolated cell expressing a TLR responsive to the known TLR ligand, and measuring the test activity involves contacting the test composition with the isolated cell expressing the TLR responsive to the known TLR ligand. Further, in one embodiment the isolated cell expressing the TLR responsive to the known TLR ligand includes an expression vector for the TLR responsive to the known TLR ligand. Such expression vector, and likewise for any expression vector according to the instant invention, can be introduced into the cell using any suitable method.

In one embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand naturally expresses the TLR responsive to the known TLR ligand. Such a cell can be naturally occurring or it can be a cell line, provided the cell does not include an expression vector introduced into the cell for the purpose of artificially inducing the cell to express or overexpress the TLR.

In one particular embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226. In another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is Raji, RAMOS, Nalm, THP-1 or KG-1 and the TLR is TLR9. In another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226, Raji or RAMOS and the TLR is TLR7. In yet another embodiment, the isolated cell expressing the TLR responsive to the known TLR ligand is a KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a Hela cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell and the TLR is TLR3.

Further according to this aspect of the invention, in one embodiment measuring the reference activity and measuring the test activity each comprises measuring signaling activity mediated by a TLR responsive to the known TLR ligand. As described in greater detail elsewhere herein, TLR signaling involves a series of intracellular signaling events. These signaling events give rise to various downstream products, including certain transcription

factors (e.g., NF-κB and AP-1), cytokines, chemokines, etc., which can affect the activity of certain gene promoters. For example, in one embodiment the signaling activity is activity of a reporter gene or reporter construct under the control of a NF-κB response element.

In other embodiments, the signaling activity is activity of a reporter gene or reporter construct under the control of an interferon-stimulated response element (ISRE); an IFN-α promoter; an IFN-β promoter; an IL-6 promoter; an IL-8 promoter; an IL-12 p40 promoter; a RANTES promoter; an IL-10 promoter or an IP-10 promoter.

In one embodiment, the known TLR ligand is an immunostimulatory nucleic acid. An immunostimulatory nucleic acid can include, without limitation, a CpG nucleic acid. In another embodiment, the known TLR ligand is an immunoinhibitory nucleic acid. When the known TLR ligand is a TLR antagonist (e.g., an immunoinhibitory oligonucleotide), the method according to this aspect of the invention can further involve measuring the reference activity of the reference composition and measuring the test activity of the test composition, each performed in the presence of a known immunostimulatory TLR ligand.

In various embodiments, the known TLR ligand is a ligand for a particular TLR. Thus in one embodiment the known TLR ligand is a TLR9 ligand. More specifically, in one embodiment the known TLR ligand is a CpG nucleic acid.

In one embodiment, the known TLR ligand is a TLR3 ligand. Such a ligand can include, for example, a double-stranded RNA or a homolog thereof.

In one embodiment, the known TLR ligand is a TLR7 ligand. In one embodiment the known TLR ligand is a TLR8 ligand.

The invention provides in another aspect a method for quality assessment of a test lot of a pharmaceutical product containing a known TLR9 ligand. The method according to this aspect of the invention involves measuring a reference activity of a reference lot of a pharmaceutical product comprising a known TLR9 ligand, wherein the known TLR9 ligand is a nucleic acid molecule; measuring a test activity of a test lot of a pharmaceutical product comprising the known TLR9 ligand; comparing the test activity to the reference activity; and rejecting the test lot if the test activity falls outside of a predetermined range of variance about the reference activity.

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGT CGT TTT GTC GTT-3' (SEQ ID NO:1).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGA CGT TTT GTC GTT-3' (SEQ ID NO:139).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TGT CGT TTT TTT CGA-3' (SEQ ID NO:140).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT CGT CGT TTC GTC GTT-3' (SEQ ID NO:141).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT CGT CGT TTT GTC GTT-3' (SEQ ID NO:142).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TTC GGT CGT TTT-3' (SEQ ID NO:143).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TTC GTG CGT TTT T-3' (SEQ ID NO:144).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TCG TTT TCG GCG GCC GCC G-3' (SEQ ID NO:145).

In one embodiment according to this aspect of the invention, the known TLR9 ligand is an oligonucleotide having a base sequence provided by 5'-TCG TC_G TTT TAC_GGC GCC_GTG CCG-3' (SEQ ID NO:146), wherein every internucleoside linkage is phosphorothioate except for those indicated by "_", which are phosphodiester.

Each of the limitations of the invention can encompass various embodiments of the invention. It is, therefore, anticipated that each of the limitations of the invention involving any one element or combinations of elements can be included in each aspect of the invention.

Brief Description of the Figures

Fig. 1 is a bar graph showing cell surface expression of various markers by RPMI 8226 24 hours and 48 hours following stimulation with CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), LPS and IL-1.

Fig. 2 is a bar graph showing IL-8 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 3 is a bar graph showing IL-6 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 4 is a bar graph showing IP-10 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 5 is a bar graph showing IL-10 production by RPMI 8226 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1), non-CpG nucleic acid (SEQ ID NO: 2), R-848 and LPS.

Fig. 6 is a dose response curve showing fold induction of IL-8 production 24 hours after exposure to CpG nucleic acid (SEQ ID NO: 1) and non-CpG nucleic acid (SEQ ID NO: 2). The EC_{50} for CpG nucleic acid is 19 nM and the EC_{50} for non-CpG nucleic acid is 263 nM.

Fig. 7 is a bar graph showing NF-κB activation in RPMI 8226 transfected transiently with a NF-κB-luciferase reporter gene construct as a function of cell density and nucleic acid amount transfected, following exposure to CpG nucleic acid (SEQ ID NO: 1), LPS and TNF-α. NF-κB activation is measured by luciferase activity.

Fig. 8 is a bar graph showing RT-PCR results from RNA isolated from RPMI 8226 using gene specific primers for TLR7, TLR8 and TLR9 genes.

Fig. 9 is a dose response curve showing IP-10 production induced by SEQ ID NO: 1, and inhibition thereof in the presence of SEQ ID NO: 151, a immunoinhibitory nucleic acid.

Fig. 10 is a bar graph showing the results of a TLR9 RT-PCR analysis of a number of cell lines.

Fig. 11 is a bar graph showing the results of a TLR7 RT-PCR analysis of a number of cell lines.

Fig. 12 is a bar graph showing the results of a TLR3 RT-PCR analysis of a number of cell lines.

Fig. 13 is a bar graph showing the results of a TLR3, TLR7, TLR8 and TLR9 RT-PCR analysis of the Raji cell line.

Fig. 14 is a graph showing IL-6 production by the Raji cell line upon stimulation with various ODN (SEQ ID NO:1; SEQ ID NO:154; SEQ ID NO:158; SEQ ID NO:160; SEQ ID NO:159; SEQ ID NO:161).

Fig. 15 is a bar graph showing IL-6 production of the Raji cell line upon stimulation with poly I:C and R-848.

Fig. 16 is a bar graph showing IFN-α2 production by the Raji cell line upon stimulation with CpG ODN (SEQ ID NO: 1), R-848 and poly I:C.

Fig. 17 is a bar graph showing CD80 expression (by flow cytometry) by the RAMOS cell line upon stimulation with CpG ODN (SEQ ID NO: 1) and non-CpG ODN (SEQ ID NO: 2).

Fig. 18A is a bar graph showing the induction of NF-κB by 293 fibroblast cells transfected with human TLR9 in response to exposure to various stimuli, including CpG-ODN, GpC-ODN, LPS, and medium.

Fig. 18B is a bar graph showing the amount of IL-8 produced by 293 fibroblast cells transfected with human TLR9 in response to exposure to various stimuli, including CpG-ODN, GpC-ODN, LPS, and medium.

Fig. 19 is a bar graph showing the induction of NF-κB-luc produced by stably transfected 293-mTLR9 cells in response to exposure to various stimuli, including CpG-ODN, methylated CpG-ODN (Me-CpG-ODN), GpC-ODN, LPS and medium.

Fig. 20 is a bar graph showing the induction of NF-κB-luc produced by stably transfected 293-hTLR9 cells in response to exposure to various stimuli, including CpG-ODN, methylated CpG-ODN (Me-CpG-ODN), GpC-ODN, LPS and medium.

Fig. 21 is a series of gel images depicting the results of reverse transcriptase-polymerase chain reaction (RT-PCR) assays for murine TLR9 (mTLR9), human TLR9 (hTLR9), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in untransfected control 293 cells, 293 cells transfected with mTLR9 (293-mTLR9), and 293 cells transfected with hTLR9 (293-hTLR9).

It is to be understood that the Figures are not required for enablement of the invention.

Brief Description of Sequences

SEQ ID NO:1 is the nucleotide sequence of an immunostimulatory nucleic acid (TLR9 ligand).

SEQ ID NO:2 is the nucleotide sequence of a non-CpG nucleic acid.

SEQ ID NO:3 is the nucleotide sequence of human TLR2 cDNA (U88878).

SEQ ID NO:4 is the amino acid sequence of human TLR2 protein (AAC34133).

SEQ ID NO:5 is the nucleotide sequence of murine TLR2 cDNA (AF165189).

SEQ ID NO:6 is the amino acid sequence of murine TLR2 protein (NP_036035).

SEQ ID NO:7 is the nucleotide sequence of human TLR3 cDNA (NM_003265).

SEQ ID NO:8 is the amino acid sequence of human TLR3 protein (NP_003256).

SEQ ID NO:9 is the nucleotide sequence of murine TLR3 cDNA (AF355152).

SEQ ID NO:10 is the amino acid sequence of murine TLR3 protein (AAK26117).

SEQ ID NO:11 is the nucleotide sequence of human TLR4 cDNA (U88880).

SEQ ID NO:12 is the nucleotide sequence of human TLR4 cDNA transcript variant 4 (NM_138557).

SEQ ID NO:13 is the nucleotide sequence of human TLR4 cDNA transcript variant 2 (NM_138556).

SEQ ID NO:14 is the nucleotide sequence of human TLR4 cDNA transcript variant 1 (NM_138554).

SEQ ID NO:15 is the nucleotide sequence of human TLR4 cDNA transcript variant 3 (NM_003266).

SEQ ID NO:16 is the amino acid sequence of human TLR4 protein isoform A (NP_612564).

SEQ ID NO:17 is the amino acid sequence of human TLR4 protein isoform B (NP_612566).

SEQ ID NO:18 is the amino acid sequence of human TLR4 protein isoform C (NP_003257).

SEQ ID NO:19 is the amino acid sequence of human TLR4 protein isoform D (NP_612567).

SEQ ID NO:20 is the nucleotide sequence of murine TLR4 cDNA (NM_021297).

SEQ ID NO:21 is the nucleotide sequence of murine TLR4 mRNA (AF185285).

SEQ ID NO:22 is the nucleotide sequence of murine TLR4 mRNA (AF110133).

SEQ ID NO:23 is the amino acid sequence of murine TLR4 protein (AAD29272).

SEQ ID NO:24 is the amino acid sequence of murine TLR4 protein (AAF04278).

SEQ ID NO:25 is the nucleotide sequence of human TLR5 cDNA (AB060695).

SEQ ID NO:26 is the amino acid sequence of human TLR5 protein (BAB43558).

SEQ ID NO:27 is the amino acid sequence of human TLR5 protein (O60602).

SEQ ID NO:28 is the amino acid sequence of human TLR5 protein (AAC34136).

SEQ ID NO:29 is the nucleotide sequence of murine TLR5 cDNA (AF186107).

SEQ ID NO:30 is the amino acid sequence of murine TLR5 protein (AAF65625).

SEQ ID NO:31 is the nucleotide sequence of human TLR7 cDNA (AF240467).

SEQ ID NO:32 is the nucleotide sequence of human TLR7 cDNA (AF245702).

SEQ ID NO:33 is the nucleotide sequence of human TLR7 cDNA (NM_016562).

SEQ ID NO:34 is the amino acid sequence of human TLR7 protein (AAF60188).

SEQ ID NO:35 is the amino acid sequence of human TLR7 protein (AAF78035).

SEQ ID NO:36 is the amino acid sequence of human TLR7 protein (NP_057646).

SEQ ID NO:37 is the amino acid sequence of human TLR7 protein (Q9NYK1).

SEQ ID NO:38 is the nucleotide sequence of murine TLR7 cDNA (AY035889).

SEQ ID NO:39 is the nucleotide sequence of murine TLR7 splice variant (NM_133211).

SEQ ID NO:40 is the nucleotide sequence of murine TLR7 splice variant (AF334942).

SEQ ID NO:41 is the amino acid sequence of murine TLR7 protein (AAK62676).

SEQ ID NO:42 is the amino acid sequence of murine TLR7 protein (AAL73191).

SEQ ID NO:43 is the amino acid sequence of murine TLR7 protein (AAL73192).

SEQ ID NO:44 is the amino acid sequence of murine TLR7 protein (NP_573474).

SEQ ID NO:45 is the amino acid sequence of murine TLR7 protein (P58681).

SEQ ID NO:46 is the nucleotide sequence of human TLR8 cDNA (AF245703).

SEQ ID NO:47 is the nucleotide sequence of human TLR8 cDNA (AF246971).

SEQ ID NO:48 is the nucleotide sequence of human TLR8 cDNA (NM_138636).

SEQ ID NO:49 is the nucleotide sequence of human TLR8 cDNA (NM_016610).

SEQ ID NO:50 is the amino acid sequence of human TLR8 protein (AAF78036).

SEQ ID NO:51 is the amino acid sequence of human TLR8 protein (AAF64061).

SEQ ID NO:52 is the amino acid sequence of human TLR8 protein (Q9NR97).

SEQ ID NO:53 is the amino acid sequence of human TLR8 protein (NP_619542).

SEQ ID NO:54 is the amino acid sequence of human TLR8 protein (NP_057694).

SEQ ID NO:55 is the nucleotide sequence of murine TLR8 cDNA (AY035890).

SEQ ID NO:56 is the nucleotide sequence of murine TLR8 cDNA (NM_133212).

SEQ ID NO:57 is the amino acid sequence of murine TLR8 protein (AAK62677).

SEQ ID NO:58 is the amino acid sequence of murine TLR8 protein (NP_573475).

SEQ ID NO:59 is the amino acid sequence of murine TLR8 protein (P58682).

SEQ ID NO:60 is the nucleotide sequence of human TLR9 cDNA (AF245704).

SEQ ID NO:61 is the nucleotide sequence of human TLR9 cDNA (AB045180).

SEQ ID NO:62 is the amino acid sequence of human TLR9 protein (AAF78037).

SEQ ID NO:63 is the amino acid sequence of human TLR9 protein (AAF72189).

SEQ ID NO:64 is the amino acid sequence of human TLR9 protein (AAG01734).

SEQ ID NO:65 is the amino acid sequence of human TLR9 protein (AAG01735).

SEQ ID NO:66 is the amino acid sequence of human TLR9 protein (AAG01736).

SEQ ID NO:67 is the amino acid sequence of human TLR9 protein (BAB19259).

SEQ ID NO:68 is the nucleotide sequence of murine TLR9 cDNA (AF348140).

SEQ ID NO:69 is the nucleotide sequence of murine TLR9 cDNA (AB045181).

SEQ ID NO:70 is the nucleotide sequence of murine TLR9 cDNA (AF314224).

SEQ ID NO:71 is the nucleotide sequence of murine TLR9 cDNA (NM_031178).

SEQ ID NO:72 is the amino acid sequence of murine TLR9 protein (AAK29625).

SEQ ID NO:73 is the amino acid sequence of murine TLR9 protein (AAK28488).

SEQ ID NO:74 is the amino acid sequence of murine TLR9 protein (BAB19260).

SEQ ID NO:75 is the amino acid sequence of murine TLR9 protein (NP_112455).

SEQ ID NO:76 is the nucleotide sequence of human TLR10 cDNA (AF296673).

SEQ ID NO:77 is the amino acid sequence of human TLR10 protein (AAK26744).

SEQ ID NO:78 is the nucleotide sequence of human TLR6 cDNA (AB020807).

SEQ ID NO:79 is the nucleotide sequence of human TLR6 mRNA (NM_006068).

SEQ ID NO:80 is the amino acid sequence of human TLR6 protein (BAA78631).

SEQ ID NO:81 is the amino acid sequence of human TLR6 protein (NP_006059).

SEQ ID NO:82 is the amino acid sequence of human TLR6 protein (Q9Y2C9).

SEQ ID NO:83 is the nucleotide sequence of murine TLR6 cDNA (AB020808).

SEQ ID NO:84 is the nucleotide sequence of murine TLR6 cDNA (NM_011604).

SEQ ID NO:85 is the nucleotide sequence of murine TLR6 cDNA (AF314636).

SEQ ID NO:86 is the amino acid sequence of murine TLR6 protein (BAA78632).

SEQ ID NO:87 is the amino acid sequence of murine TLR6 protein (AAG38563).

SEQ ID NO:88 is the amino acid sequence of murine TLR6 protein (NP_035734).

SEQ ID NO:89 is the amino acid sequence of murine TLR6 protein (Q9EPW9).

SEQ ID NO:90 is the nucleotide sequence of a consensus sequence for NF-κB p50 subunit.

SEQ ID NO:91 is the nucleotide sequence of a consensus sequence for NF-κB p65 subunit.

SEQ ID NO:92 is the nucleotide sequence of an example of an NF-κB p65 subunit binding site.

SEQ ID NO:93 is the nucleotide sequence of an example of a murine CREB binding site.

SEQ ID NO:94 is the nucleotide sequence of an example of a murine AP-1 binding site.

SEQ ID NO:95 is the nucleotide sequence of an example of a murine AP-1 binding site.

SEQ ID NO:96 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:97 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:98 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:99 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:100 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:101 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:102 is the nucleotide sequence of an example of an ISRE.

SEQ ID NO:103 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:104 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:105 is the nucleotide sequence of an example of an SRE.

SEQ ID NO:106 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:107 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:108 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:109 is the nucleotide sequence of an example of an NFAT binding site.

SEQ ID NO:110 is the nucleotide sequence of an example of a GAS.

SEQ ID NO:111 is the nucleotide sequence of a p53 binding site consensus sequence.

SEQ ID NO:112 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:113 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:114 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:115 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:116 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:117 is the nucleotide sequence of an example of a p53 binding site.

SEQ ID NO:118 is the nucleotide sequence of an example of a TARE (TNF-α response element).

SEQ ID NO:119 is the nucleotide sequence of an example of an SRF binding site.

SEQ ID NO:120 is the nucleotide sequence of an example of an SRF binding site.

SEQ ID NO:121 is the nucleotide sequence of the -620 to +50 promoter region of IFN-α4.

SEQ ID NO:122 is the nucleotide sequence of the -140 to +9 promoter region of IFN-α1.

SEQ ID NO:123 is the nucleotide sequence of the -140 to +9 promoter region of IFN-α1 (point mutation, AL353732).

SEQ ID NO:124 is the nucleotide sequence of the -280 to +20 promoter region of IFN-β.

SEQ ID NO:125 is the nucleotide sequence of the -397 to +5 promoter region of human RANTES (AB023652).

SEQ ID NO:126 is the nucleotide sequence of the -751 to +30 promoter region of human IL-12 p40.

SEQ ID NO:127 is the nucleotide sequence of the -250 to +30 promoter region of human IL-12 p40.

SEQ ID NO:128 is the nucleotide sequence of the -288 to +7 promoter region of human IL-6.

SEQ ID NO:129 is the nucleotide sequence of the IL-6 gene promoter from -1174 to +7 (M22111).

SEQ ID NO:130 is the nucleotide sequence of the -734 to +44 promoter region derived from human IL-8.

SEQ ID NO:131 is the nucleotide sequence of the -162 to 44 promoter region of human IL-8.

SEQ ID NO:132 is the nucleotide sequence of the -615 to +30 promoter region of human TNF-α.

SEQ ID NO:133 is the nucleotide sequence of a promoter region of human TNF-β.

SEQ ID NO:134 is the nucleotide sequence of the -875 to +97 promoter region of human IP-10.

SEQ ID NO:135 is the nucleotide sequence of the -219 to +114 promoter region of human CXCL11 (IP-9).

SEQ ID NO:136 is the nucleotide sequence of the full length promoter region of human CXCL11 (IP-9).

SEQ ID NO:137 is the nucleotide sequence of the -289 to +217 promoter region of IGFBP4 (Insulin growth factor binding protein 4).

SEQ ID NO:138 is the nucleotide sequence of the full length promoter region of IGFBP4.

SEQ ID NO:139 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:140 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:141 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:142 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:143 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:144 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:145 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:146 is the nucleotide sequence of an immunostimulatory nucleic acid.

SEQ ID NO:147 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

SEQ ID NO:148 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

SEQ ID NO:149 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

SEQ ID NO:150 is the nucleotide sequence of an immunostimulatory methylated CpG nucleic acid.

SEQ ID NO:151 is the nucleotide sequence of an immunoinhibitory nucleic acid.

SEQ ID NO:152 is the nucleotide sequence of a sense primer for human TLR3.

SEQ ID NO:153 is the nucleotide sequence of an antisense primer for human TLR3.

SEQ ID NO:154 is the nucleotide sequence of a GpC nucleic acid.

SEQ ID NO:155 is the nucleotide sequence of a CpG ODN.

SEQ ID NO:156 is the nucleotide sequence of a GpC ODN.

SEQ ID NO:157 is the nucleotide sequence of a Me-CpG ODN.

SEQ ID NO:158 is the nucleotide sequence of a TLR9 ligand.

SEQ ID NO:159 is the nucleotide sequence of a TLR9 ligand.

SEQ ID NO:160 is the nucleotide sequence of a TLR9 ligand.

SEQ ID NO:161 is the nucleotide sequence of a TLR9 ligand.

Detailed Description of the Invention

In its broadest sense, the invention relates to screening methods and tools to be used to identify and discriminate between newly discovered immunomodulatory molecules and to compare and standardize compositions of known immunomodulatory molecules. The immunomodulatory molecules are preferably TLR ligands.

Thus, the invention is based in part on the discovery that cell lines expressing endogenous TLR respond to TLR ligands in a manner similar to the response of peripheral blood mononuclear cells (PBMC). PBMC respond to immunomodulatory TLR ligands by modulating one or more parameters including gene expression, cell surface marker expression, cytokine and/or chemokine production and secretion, cell cycle status, phosphorylation status, and the like. TLR ligands can be categorized and distinguished based on the cellular changes they induce (i.e., their induction profiles). The ability of a TLR ligand to provide therapeutic or prophylactic benefit to a subject depends on its induction profile. The ability to screen new TLR ligands for a panel of response indicators or parameters allows for rapid discrimination and categorization of TLR ligands. Moreover, the similarity between the cell line responses and those observed after in vivo administration of the TLR ligand indicates that the cell lines are suitable predictors of in vivo activity. The use of in vitro propagated cell lines additionally overcomes the variability encountered when using freshly isolated PBMC.

The TLR ligands identified according to the invention therefore can be used therapeutically or prophylactically in a more patient- or disorder-specific manner. The invention allows for the tailoring of TLR ligands for particular patients or disorders.

The invention identifies a number of cell lines that can be used to identify TLR ligands based on endogenous TLR expression such as TLR3, TLR7 and TLR9 expression. As an example, the invention is premised in part on the discovery of TLR9 expression in a number of cell lines including RPMI 8226, Raji, RAMOS, THP-1, Nalm-6 and KG-1. Cell lines RPMI 8226, Raji and RAMOS have been determined to express TLR7 according to the invention. Cell lines KG-1 cell, a Nalm cell, a Raji cell, a RAMOS cell, a Jurkat cell, a Hela cell, a Hep-2 cell, a Hep-2 cells, a A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell have been discovered to express TLR3 according to the invention.

It is further premised in part on the discovery that RPMI 8226 cells respond to the imidazoquinoline compound R-848. Consistent with this latter finding, it was also discovered that RPMI 8226 cells express TLR7.

The invention in other aspects provides for screening methods and tools for verifying and standardizing compositions containing known TLR ligands. These compositions may be for example commercial production lots to be used in a clinical setting. Accordingly, the invention provides methods for standardizing lots of known TLR ligands prior to distribution and use clinically. In this way, production processes can be observed and controlled and substandard production lots can be identified and eliminated prior to shipment.

The methods of the instant invention can be used at any step in the preparation and production of clinical material, i.e., pharmaceutical product. In particular, the methods will find use in characterizing or validating raw materials, in-process materials, finished product materials (e.g., pre-release materials), and post-production materials (e.g., post-release materials). The methods can also be used to validate existing process methods, as well as to validate new or changed process methods used in the production of the pharmaceutical product.

Screening Assays Generally

The screening assays provided herein may be used to identify immunomodulatory agents. Immunomodulatory agents are agents that either stimulate or inhibit immune responses in a subject. Accordingly, as used herein, immunomodulation embraces both immunostimulation and immunoinhibition.

The screening methods are used to identify TLR agonists and antagonists. The methods can also be used to identify compounds that enhance the immunostimulation induced by a TLR agonist. This latter set of compounds is referred to herein as "enhancers". A TLR agonist is a compound that stimulates TLR signaling activity. A TLR antagonist is a compound that inhibits TLR signaling activity. Agonists are generally referred to herein as immunostimulatory compounds because stimulation of TLR is associated with immune stimulation. Antagonists are generally referred to herein as immunoinhibitory compounds because inhibition of TLR is associated with immune inhibition. TLR antagonists include compounds that reduce (or eliminate completely) the immunostimulation induced by a TLR

agonist. In some embodiments, the agonists, antagonists and enhancers are TLR ligands (i.e., they bind to a TLR). In other embodiments, the test compounds with agonist, antagonist or enhancer activity may act downstream or upstream of the TLR-TLR ligand interaction.

An "immunostimulatory compound" as used herein refers to a natural or synthetic compound that characteristically induces a TLR-mediated response when contacted with a suitable functional TLR polypeptide. In one embodiment the immunostimulatory compound is a natural or synthetic compound that induces a TLR-mediated response when contacted with a cell that naturally or artificially expresses a suitable functional TLR polypeptide. Depending on the aspect of the invention, the cell may be an experimental cell or a primary cell such as a PBMC.

Examples of immunostimulatory compounds include the following immunostimulatory nucleic acids, which are discussed in further detail below:

5'-TCGTCGTTTTGTCGTTTTGTCGTT-3'	(SEQ ID NO:1)
5'-TCGTCGTTTTGACGTTTTGTCGTT-3'	(SEQ ID NO:139)
5'-TCGTCGTTTTGTCGTTTTTTTCGA-3'	(SEQ ID NO:140)
5'-TCGTCGTTTCGTCGTTTCGTCGTT-3'	(SEQ ID NO:141)
5'-TCGTCGTTTCGTCGTTTTGTCGTT-3'	(SEQ ID NO:142)
5'-TCGTCGTTTTTCGGTCGTTTT-3'	(SEQ ID NO:143)
5'-TCGTCGTTTTTCGTGCGTTTTT-3'	(SEQ ID NO:144)
5'-TCGTCGTTTTCGGCGGCCGCCG-3'	(SEQ ID NO:145)
5'-TCGTC_GTTTTAC_GGCGCC_GTGCCG-3'	(SEQ ID NO:146)

Imidazoquinolines are immune response modifiers thought to induce expression of several cytokines including interferons (e.g., IFN-α and IFN-β), TNF-α and some interleukins (e.g., IL-1, IL-6 and IL-12) as well as chemokines (e.g., IP-10 and IL-8). Imidazoquinolines are capable of stimulating a Th1 immune response, as evidenced in part by their ability to induce increases in IgG2a levels. Imidazoquinoline agents reportedly are also capable of inhibiting production of Th2 cytokines such as IL-4, IL-5, and IL-13. Some of the cytokines induced by imidazoquinolines are produced by macrophages and dendritic cells. Some species of imidazoquinolines have been reported to increase NK cell lytic activity and to stimulate B cells proliferation and differentiation, thereby inducing antibody production and secretion. Imidazoquinoline mimics can also be tested using the screening methods.

An "immunoinhibitory compound" as used herein refers to a natural or synthetic compound that characteristically inhibits a TLR-mediated response when contacted with a suitable functional TLR polypeptide. In one embodiment the immunoinhibitory compound is a natural or synthetic compound that inhibits a TLR-mediated response when contacted with a cell that naturally or artificially expresses a suitable functional TLR polypeptide.

In addition to the immunoinhibitory nucleic acids disclosed elsewhere herein, immunoinhibitory compounds and TLR antagonists encompass certain small molecules (chloroquine, quinacrine, 9-aminoacridines and 4-aminoquinolines, and derivatives thereof) described by Macfarlane and colleagues in U.S. Pat. 6,221,882; U.S. Pat. 6,399,630; U.S. Pat. 6,479,504; U.S. Pat. 6,521,637; and published U.S. Pat. application 2002/0151564, the contents of all of which are hereby incorporated by reference in their entirety.

The invention provides in part methods and tools that utilize cell lines, in modified or unmodified form, as surrogates for PBMC. Immunomodulation by TLR ligands can be assessed using one or preferably more parameters including but not limited to cytokine and chemokine secretion, upregulation of cell surface markers, changes in cell proliferation, phosphorylation changes, and the like. These parameters may be native readouts or artificial readouts as described herein.

The cellular response to immunostimulatory nucleic acids by the cell lines described herein (e.g., RPMI 8226, Raji, RAMOS, and the like) so resembles that of PBMC that these cells can be used to identify and differentiate between immunomodulatory compounds based on the extent of the induced response and the particular profile of that response. The invention provides a number of cell lines each with a particular endogenous TLR expression profile, as described herein.

The cell lines can be used to identify immunomodulatory compounds with particular response profiles. As an example, the cell lines can be used to identify molecules that are mimics to known TLR ligands. The cell lines can also be used to identify TLR ligands that trigger some but not necessarily all of the responses induced by known TLR ligands. For example, the cell line can be used to distinguish between compounds based on individual or group cytokine or chemokine secretion, or based on upregulation of one, a subset or all cell surface markers. As an example, in some therapeutic instances, it may be desirable to use a compound that induces the secretion of relatively high levels of chemokine such as IP-10, yet induces only relatively low levels of one or more other factors. The screening methods of the invention allow for the identification of such a compound with this type of induction profile.

It is to be understood that the screening method also can be used to determine effective amounts of known and newly identified immunomodulatory compounds. For example, the EC_{50} value of a TLR ligand for the production of a particular cytokine or chemokine can be determined, thereby facilitating comparison between different nucleic acids.

Generally, these assays require the incubation of cells with a reference compound and a test compound, and an analysis of the readout. Depending on the embodiment, the same cells are exposed to the reference compound and the test compound. An example of this latter embodiment is a screening assay for compounds that enhance the immunostimulatory effects of a TLR agonist. Another example is a screening assay for compounds that inhibit the immunostimulatory effects of a TLR agonist. In both examples, the reference compound is a positive reference compound (i.e., it is itself immunostimulatory).

In other embodiments, particularly those directed at identifying immunostimulatory compounds, separate aliquots from the same cell line (or from the same freshly harvested cell population) are exposed to either the reference compound or the test compound, and the readouts from each are measured and compared to the other. If the reference compound is a negative reference compound (i.e., it is inert and neither immunostimulatory nor immunoinhibitory), then any test level that is greater than the reference level is indicative of a test compound that has at least some immunostimulatory capacity. Generally, the negative reference compound is used to set background levels of immunostimulation or immunoinhibition observed in the absence of the test compound. If the reference compound is a positive reference compound (i.e., it is immunostimulatory), then it is possible to compare and contrast the induction profile of the test compound to that of the reference compound.

In some instances, separate reference assays individually containing a positive and a negative reference compound are performed alongside the test assay. For example, if the test assay is a screen for an immunostimulatory TLR ligand, then reference assays can be a positive reference assay (in which the reference compound is immunostimulatory), a negative reference assay (in which the reference compounds is immunologically inert or neutral), or both. A test compound is defined as immunostimulatory if it induces a response greater than that of the negative reference compound. The level and profile of the immunostimulatory response can be compared to the level and profile induced by the positive reference compound. It is to be understood that a test compound that induces a level of immunostimulation less than that of the positive reference compound may still be considered immunostimulatory according to the invention. Modifications to these screening assays for a

desired readout will be apparent to those of ordinary skill in the are based on the teachings provided herein.

If the test assay is a screen for an immunoinhibitory TLR ligand, then the assay may generally involve co-incubation of the test compound and a positive reference compound. The control assay may include co-incubation of the negative and positive reference compounds. As used herein, co-incubation embraces simultaneous or consecutive addition of the reference and test compounds. The test compound may be added before or after the positive reference compound. An immunoinhibitory test compound may be identified by a diminution of the immunostimulatory response induced by the positive reference compound when in the presence of the test compound. If the level of the response is less in the presence of the test compound, this indicates that the test compound is capable of interfering with the immunostimulatory effects of the positive reference compound. As an example, simultaneous or consecutive addition of a putative immunoinhibitory test compound can reduce the amount of cytokines or chemokines secreted by cells in response to the positive reference compound alone, indicating an inhibition of the immunostimulatory effects of the positive reference compound.

The reference immunoinhibitory compound can be used at one or more concentrations in conjunction with a selected or constant concentration of reference immunostimulatory compound. Under proper conditions, the immunostimulatory effect of the reference immunostimulatory compound will be less in the presence of the immunoinhibitory substance than in the absence of the immunoinhibitory substance. Furthermore, under proper conditions, the immunostimulatory effect of the reference immunostimulatory compound will decrease with increasing concentration of the immunoinhibitory substance.

The breadth of response by the cell line to immunomodulatory compounds, and its facile manipulation, allows for the identification of novel compounds. The cell line allows the rapid discovery of such compounds given that is lends itself to high throughput screening methods such as those provided herein. These methods and compositions are described in greater detail below. The invention therefore provides screening methods that utilize cell lines that either endogenous express TLRs such as the RPMI 8226 cell line as well as cell lines that have been modified to express TLRs. The invention further provides compositions that comprise such cell lines.

The verification and standardization methods of the invention generally involve assays in which an isolated cell expressing a functional TLR is contacted with each of two

compositions, each composition containing a known ligand for the TLR. One composition is a reference composition, and the assay using the reference composition yields a reference activity. The second composition is a test composition, and the assay using the test composition yields a test activity. The two contacting steps can be performed on separate cells that are alike, and typically will be performed on separate populations of cells that are alike. For example, the separate cells or the separate populations of cells can be drawn from a single population of cells. In typical usage according to this embodiment, the reference and test activities are measured essentially concurrently, although the use of historical reference activity is also contemplated by the methods of the invention. As an alternative, the two contacting steps can be performed on a single cell or on a single population of cells, usually in an essentially concurrent manner when it is desirable to have competition between reference and test compositions. In one embodiment the known TLR ligand is a nucleic acid molecule.

The assays of the invention are performed under specific conditions so that comparison can be made between reference and test activities or levels. The results of the comparison can be used as a basis upon which to accept or reject the test material as suitable for its intended use.

The biological characterization of the reference composition will generally entail a series of biological activity measurements of the reference composition using a single assay under defined conditions in order to define a range of inter-test variance. The range of inter-test variance so obtained using reference composition can be used to define an acceptable range of variance within which a subsequent test measurement must fall in order to satisfy quality standards. Such a range of acceptable variance can serve as a basis for developing predetermined range of variance about the reference activity, i.e., acceptance criteria for a particular test composition or test lot. For example, a particular reference composition can be assayed under defined conditions in a number of independent measurements and found to yield a result expressed as 100 ± 5 units of activity. Under this same example, a subsequent test measurement of a test composition performed using the same assay and defined conditions is found to yield 97 units of activity. The activity of the test composition under this example thus yielded a result that falls within the normal range of inter-test variance observed for the reference composition. Accordingly, the test material under this example could be selected on the basis of the test activity falling within a predetermined range of variance about the reference activity. In short, the test material can be deemed acceptable

provided the test activity falls within a predetermined range of activity that is related to the activity of the reference material.

In one embodiment, the methods of the invention provide for comparison between a reference lot of a particular TLR ligand and a test lot of the same particular TLR ligand. Such comparison is useful for quality control assessment of the test lot of material, also referred to herein as validation, e.g., product validation. Such comparison is also useful for process validation.

In another embodiment, the methods of the invention provide for comparison between a reference lot of a particular TLR ligand and a test lot of a different TLR ligand. In a simple example, where a test TLR ligand (T) is expected to have little or no activity characteristic of reference TLR ligand (R), comparison can be made between T and R to confirm the lack of R-like activity possessed by T. In a more complex example, where a test TLR ligand (C) is capable of exerting two different effects, wherein each effect is characteristic of one of two different classes of TLR ligand and is best characterized by one of two different reference TLR ligands (A and B), the test TLR ligand (C) can be compared with either of the two reference TLR ligands (A or B). In this second example, test composition C could be found, for example, to possess 50 percent A-like activity compared with reference A and 70 percent B-like activity compared with reference B. Test composition C could thus independently meet or fail to meet predetermined standards for each of A-like activity and B-like activity. Such comparison is also useful for quality control assessment of the test lot of material, e.g., product validation. Of course test TLR ligand C can alternatively or additionally be compared against reference TLR ligand C, as described in the preceding paragraph.

To facilitate the methods of the invention, certain conditions for carrying out the assays are standardized and used for measurements of both reference activity and test activity. In this way direct comparison between reference activity and test activity can be made readily. Conditions that can be standardized and used in this manner can include, without limitation, readout, temperature, media characteristics, duration (time between introduction of reference composition or test composition and activity measurement), methods of sampling, etc. In some embodiments the methods of the invention can be at least partially automated in order to increase throughput and/or to reduce inter-test variability. For example, robotic devices and workstations with the capacity to dispense and/or sample fluids in a set or programmable fashion are now well known in the art and can be used in performing the methods of the instant invention.

In one embodiment a standard curve of reference composition activity is employed. Typically the standard curve is generated by selecting conditions including concentration of the reference composition such that the dose-response curve is essentially linear (and the slope is non-zero) over a range of concentrations that includes the effective concentration at which activity is 50 percent of maximum (EC50). In one embodiment the standard curve spans a range of concentrations defined by EC50 ± 1 log concentration, e.g., 1×10^{-7} M – 1×10^{-5} M, where EC50 is 1×10^{-6} M. In another embodiment the standard curve spans a broader range of concentrations defined by EC50 ± 2 log concentration, e.g., 1×10^{-8} M – 1×10^{-4} M, where EC50 is 1×10^{-6} M. In yet another embodiment the standard curve spans a narrower range of concentrations defined by EC50 ± 0.5 log concentration, e.g., 3.16×10^{-7} M – 3.16×10^{-6} M, where EC50 is 1×10^{-6} M. The foregoing embodiments are intended to be exemplary and not limiting in any way. One of skill in the art will be able to select, for a given reference composition and without undue experimentation, an appropriate range of concentrations about some middle value in order to generate an essentially linear standard curve with a non-zero slope.

In one embodiment a non-linear standard curve of reference and test composition activity is employed. The standard curve can be generated by selecting conditions including concentrations of the reference composition such that the dose-response curve is sigmoidal and the EC50 value can be determined. Comparison of reference and test activity can be done by comparing, e.g., the EC50 values of both curves. Concentration range is chosen to yield a complete sigmoidal response, e.g., concentration should include EC50 ± 3 log concentration or EC50 ± 4 log concentration. In the case of testing an inhibitory compound the value determined would be the IC50, i.e., concentration where inhibition of the stimulatory signal is half-maximal.

The methods of the invention can be adapted to be automated or at least partially automated methods, as well as to parallel array or high throughput format methods. For example, the assays can be set up using multiwell plates in which cells are dispensed in individual wells and reagents are added in a systematic manner using a multiwell delivery device suited to the geometry of the multiwell plate. Manual and robotic multiwell delivery devices suitable for use in a high throughput screening assay are known by those skilled in the art. Each well or array element can be mapped in a one-to-one manner to a particular test condition, such as the test compound. Readouts can also be performed in this multiwell array, preferably using a multiwell plate reader device or the like. Examples of such devices are

known in the art and are available through commercial sources. Sample and reagent handling can be automated to further enhance the throughput capacity of the screening assay, such that dozens, hundreds, thousands, or even millions of parallel assays can be performed in a day or in a week. Fully robotic systems are known in the art for applications such as generation and analysis of combinatorial libraries of synthetic compounds. See, for example, U.S. Pat. Nos. 5,443,791 and 5,708,158.

Cell lines

The screening methods may use experimental cells. As used herein, an experimental cell is a non-primary cell (i.e., it is not a cell that has been recently harvested from a subject). It excludes, for example, freshly harvested PBMCs. An experimental cell includes a cell from a cell line such as the RPMI 8226 cell line.

In certain embodiments, the cell naturally expresses a functional TLR. In one embodiment relating to the verification and standardization aspects of the invention, the cell may be a PBMC, preferably a PBMC freshly harvested from a subject.

Cells that would be suitable for identification of TLR agonists, antagonists or enhancers according to the invention may possess one or more particular attributes. These attributes include but are not limited to being of human origin, being an immortalized stable cell line, endogenously expressing at least one functional TLR or a combination of functional TLRs, having intact signaling mechanisms, having intact uptake mechanisms, being able to upregulate cytokines, chemokines or cell surface markers, deriving from normal human B cells or from myeloma or B cell leukemia, deriving from human plasmacytoid and myeloid dendritic cells, and readily activatable by TLR ligands such as TLR7 ligands, TLR8 ligands or TLR9 ligands such as CpG nucleic acids or nucleic acids having other immunostimulatory sequence motifs or small molecules such as imidazoquinoline compounds.

In some embodiments, the cell line is the Raji cell line which expresses TLR3, TLR7 and TLR9. This latter cell line secretes, for example, IL-6 and IFN-$\alpha 2$ upon CpG nucleic acid exposure. In other embodiments, the cell line is RPMI 8226 which expresses TLR7 and TLR9. Upon CpG nucleic acid exposure, this cell line expresses, produces and/or secretes IL-8, IL-10, IP-10 and TNF-α. It also expresses at its cell surface CD86, HLA-DR and CD71. In yet other embodiments, the cell line is the RAMOS cell line which expresses TLR3, TLR7 and TLR9. This cell line at least induces CD80 cell surface expression in response to CpG nucleic acid exposure.

The cell lines have been observed to respond in a concentration dependent manner to TLR ligands such as but not limited to CpG nucleic acids and some non-CpG nucleic acids including T-rich nucleic acids, poly-T nucleic acids and poly-G nucleic acids. The highest responses have been observed using CpG nucleic acids.

The screening methods employ a variety of cell lines as shown in the Examples. These include A549 (human lung carcinoma, ATCC CCL-185), BeWo (human choriocarcinoma, ATCC CCL-98), HeLa (human cervix carcinoma, ATCC CCL-2), Hep-2 (human cervix carcinoma, ATCC CCL-23), KG-1 (human acute myeloid leukemia, ATCC CCL-246), MUTZ-3 (human acute myelomonocytic leukemia, German Collection of Cell lines and Microorganisms (DSZM) ACC-295), Nalm-6 (human B cell precursor leukemia, DSZM ACC-128), NK-92 (human Natural killer cell line, ATCC CRL-2407), NK-92 MI (IL-2 independent human Natural killer cell line, ATCC CRL-2408), Raji (human B lymphocyte Burkitt's lymphoma, ATCC CCL-86), RAMOS (B lymphocyte Burkitt's lymphoma, ATCC CRL-1596), RPMI 8226 (human B lymphocyte multiple myeloma, ATCC CCL-155), THP-1 (human acute monocytic leukemia, ATCC TIB 202), U937 (human lymphoma, ATCC CRL-1593.2) and Jurkat (human T cell leukemia, ATCC TIB 152).

As shown in the Examples, each of the afore-mentioned cell lines has a particular endogenous TLR expression profile which dictates its suitability in a particular screening assay.

A cell that artificially expresses a functional TLR can be a cell that does not express the functional TLR but for a transfected TLR expression vector. For example, human 293 fibroblasts (ATCC CRL-1573) do not express TLR7, TLR8 or TLR9, and they express very little TLR3. As described in the examples below, such cells can be transiently or stably transfected with suitable expression vector (or vectors) so as to yield cells that do express TLR3, TLR7, TLR8, TLR9, or any combination thereof. Alternatively, a cell that artificially expresses a functional TLR can be a cell that expresses the functional TLR at a significantly higher level with the TLR expression vector than it does without the TLR expression vector. Transfected cells are considered modified cells, as used herein.

A cell that artificially expresses an expression or reporter construct is preferably stably transfected.

<u>RPMI</u>

The RPMI 8226 cell line is a human multiple myeloma cell line. The cell line was established from the peripheral blood of a 61 year old man at the time of diagnosis for multiple myeloma (IgG lambda type). RPMI 8226 was previously reported as responsive to CpG nucleic acids as evidenced by the production and secretion of IL-6 protein and production of IL-12p40 mRNA. (Takeshita et al. (2000), Eur. J. Immunol. 30, 108-116, and Takeshita et al. (2000) *Ibid.* 30, 1967-1976) Takeshita et al. however used the cell line solely to study promoter constructs in order to identify transcription factor binding sites important for CpG nucleic acid signaling. It is now known according to the invention that the cell line produces a number of other chemokines and cytokines including IL-8, IL-10 and IP-10. It has also been discovered according to the invention that the cell line responds to immunostimulatory nucleic acids by upregulating cell surface expression of particular markers. Many of these markers, including CD71, CD86 and HLA-DR, are similarly upregulated in PBMCs exposed to immunostimulatory nucleic acids. This has been observed using flow cytometric analysis of the cell line following CpG nucleic acid exposure. In other aspects of the invention, the cell line can be used in similar screening assays that involve secretion of IL-6, IL-12 and/or TNF-α.

It has recently been discovered that R-848 mediates its immunostimulatory effects via other TLR family members, namely TLR7 and TLR8. TLR7 has previously been found expressed on human B cells. It has now also been discovered according to the invention that RPMI 8226 expresses TLR9 as well as TLR7, thus making it a suitable cell line for identifying immunostimulatory nucleic acid and/or imidazoquinoline (e.g., R-848) mimics or other small molecules that also signal through TLR7 and/or TLR9. Incubation of RPMI 8226 cells with the imidazoquinoline R-848 (Resiquimod) induces for example IL-8, IL-10 and IP-10 production.

<u>Known TLR Ligands</u>

Ligands for many but not all of the TLRs have been described. For instance, it has been reported that TLR1 and TLR2 signals in response to peptidoglycan and lipopeptides. Yoshimura A et al. (1999) *J Immunol* 163:1-5; Brightbill HD et al. (1999) *Science* 285:732-6; Aliprantis AO et al. (1999) *Science* 285:736-9; Takeuchi O et al. (1999) *Immunity* 11:443-51; Underhill DM et al. (1999) *Nature* 401:811-5. TLR4 has been reported to signal in response to lipopolysaccharide (LPS). Hoshino K et al. (1999) *J Immunol* 162:3749-52; Poltorak A et al. (1998) *Science* 282:2085-8; Medzhitov R et al. (1997) *Nature* 388:394-7. Bacterial

flagellin has been reported to be a natural ligand for TLR5. Hayashi F et al. (2001) *Nature* 410:1099-1103. TLR6, in conjunction with TLR2, has been reported to signal in response to proteoglycan. Ozinsky A et al. (2000) *Proc Natl Acad Sci USA* 97:13766-71; Takeuchi O et al. (2001) *Int Immunol* 13:933-40.

TLR9 is a receptor for CpG DNA. Hemmi H et al. (2000) *Nature* 408:740-5. Other TLR9 ligands are described herein under "Immunostimulatory Nucleic Acids". Certain imidazoquinoline compounds having antiviral activity are ligands of TLR7 and TLR8. Imidazoquinolines are potent synthetic activators of immune cells with antiviral and antitumor properties. R-848 is a ligand for human TLR7 and TLR8. Jurk M et al. (2002) *Nat Immunol* 3:499. Ligands of TLR3 include poly(I:C) and double-stranded RNA (dsRNA). Alexopoulou et a. (2001) Nature 413:732-738. For purposes of this invention, poly(I:C) and double-stranded RNA (dsRNA) are classified as oligonucleotide molecules. TLR3 may have a role in host defense against viruses.

Reference and Test Compounds

A test and/or reference compound can be a nucleic acid such as an oligonucleotide or a polynucleotide, an oligopeptide, a polypeptide, a lipid such as a lipopolysaccharide, a carbohydrate such as an oligosaccharide or a polysaccharide, or a small molecule. Alternatively, these compounds may also comprise or be synthesized from elements such as amino acids, carbohydrates, hormones, lipids, organic molecules, and the like.

Small molecules in general include naturally occurring, synthetic, and semisynthetic organic and organometallic compounds with molecular weight less than about 2.5 kDa. Examples of small molecules include most drugs, subunits of polymeric materials, and analogs and derivatives thereof.

Some specific examples of small molecules include the imidazoquinolines. As used herein, an imidazoquinolines include imidazoquinoline amines (imidazoquinolinamines), imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2 bridged imidazoquinoline amines. These compounds have been described in U.S. Pat. Nos. 4,689,338; 4,929,624; 5,238,944; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640; 5,395,937; 5,482,936; 5,494,916; 5,525,612; 6,039,969 and 6,110,929. Particular species of imidazoquinoline agents include resiquimod (R-848; S-28463; 4-amino-2 ethoxymethyl-α,α-dimethyl-1*H*-imidazo[4,5-c]quinoline-1-ethanol); and imiquimod (R-837; S-26308; 1-(2-methylpropyl)-1*H*-imidazo[4,5-c]quinoline-4-amine). Further examples of specific small

molecules include 4-aminoquinoline and derivatives thereof, 9-aminoacridine and derivatives thereof, and additional compounds disclosed in U.S. Pat. Nos. 6,221,882; 6,399,630; 6,479,504; and 6,521,637; and published U.S. Pat. Application No. 2002/0151564 A1, the entire contents of which are hereby incorporated by reference.

The test and reference compounds may be formulated for pharmaceutical use or not. For example, a test compound not formulated for pharmaceutical use can be a compound (e.g., a lot or batch of the compound) under evaluation for possible use in preparing a pharmaceutical formulation of the compound.

A reference compound, as used herein, is a compound having a known activity in the presence of a TLR. The reference compound may stimulate TLR signaling (and is therefore regarded as a positive reference compound), or it may be inert in the presence of a TLR (and is therefore regarded as a negative reference compound). If it is a positive reference compound, it need not be the best known stimulator of TLR signaling (i.e., it is possible that other reference compounds and even test compounds will stimulate TLR signaling to a greater extent). The readout of the screening assay may simply be stated relative to the level of signaling that occurs in the presence of the reference compound. Preferably, the reference compound is analyzed prior to the screening assay in order to determine its level of activity on a TLR. In some aspects of the invention, the reference compound and the test compound will be assayed separately (i.e., in separate wells); in other aspects, the reference compound and the test compound will be assayed together (i.e., in the same well). These latter aspects are designed to measure the ability of a test compound to modulate the activity of the reference compound. The activity of the test compound and the reference compound combined (i.e., when assayed together in the same well) may be the same as that of the positive reference compound alone, indicating at a minimum that the test compound is not inhibitory; or it may be less than that of the positive reference compound, indicating at a minimum that it is inhibitory to the effect of the reference compound; or it may be additive or synergistic possibly indicating that the test compound is an enhancer. The effect of an enhance may be due to its ability to stimulate TLR signaling independently of the positive reference compound.

A "reference composition" as used herein refers to a composition that includes a reference compound and optionally another agent, e.g., a pharmaceutically acceptable carrier and/or another biologically active agent. A reference compound may be an immunostimulatory compound or it may be an immunoinhibitory compound.

As discussed further below, in some aspects of the invention the reference compositions include both finished products, e.g., finished pharmaceutical products, as well as raw materials and other in-process materials used for the preparation of such finished products, all of which contain a known TLR ligand. As used herein, a "production lot" shall refer to a batch or lot of a completed product prepared for release as clinical material, e.g., a pharmaceutical product. As used herein, an "in-process lot" shall refer to a batch or lot of unfinished product that is prepared in the course of making a production lot; an "in-process lot" shall also refer to a batch or lot of raw material provided for use in the production of a production lot.

In some aspects of the invention, the reference compositions of the invention are highly characterized in terms of their chemical, physical, and biological properties. A reference composition will be a specific composition previously determined to have a specific activity, or range of specific activity, of the particular known TLR ligand present in the composition. As used herein, "specific activity" refers to an amount of activity per unit mass or per unit volume of the reference composition as a whole, as determined using a defined assay under defined conditions. In one embodiment the reference composition is a representative sample of a particular lot or batch of a specific TLR ligand. In one embodiment the reference composition is a representative sample of a particular lot or batch of a specific TLR ligand formulated for pharmaceutical use, e.g., a sterile solution of the TLR ligand at a determined concentration or activity.

At least the following parameters are typically very well defined for a given reference composition: chemical formula of the active ingredient TLR ligand (e.g., nucleobase sequence and type of backbone of a nucleic acid; structural formula of a small molecule); concentration; diluent composition; and purity. Such parameters as purity and concentration can be determined using any appropriate physicochemical method, e.g., optical spectroscopy including absorbance at one or more specified wavelengths; nuclear magnetic resonance (NMR) spectroscopy; mass spectrometry (MS), including matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS); melting point; specific gravity; chromatography including as appropriate high pressure liquid chromatography (HPLC), one- and two-dimensional polyacrylamide gel electrophoresis (PAGE), capillary electrophoresis, and the like; as well as other methods known to those of skill in the art.

Reference compositions can also be very well characterized in terms of their biological activity, independent of the methods of the invention, although the methods of the

invention generally include such characterization, at least in part. A reference composition can be very well characterized in terms of its biological activity by characterizing, both qualitatively and quantitatively, the response by sensitive cells to the reference composition under defined conditions. For example, a reference composition can be a specific CpG oligonucleotide such as SEQ ID NO:1 which in a specific assay and under specific conditions of temperature, concentration, duration of contact between the CpG oligonucleotide and a population of TLR9-expressing cells, and particular readout, reliably yields a specific result or range of results. Results can be expressed in any suitable manner, but can include results expressed on a per-cell basis, e.g., picograms of particular cytokine per cell per hour of contact with the reference composition. Reference compositions can be very well characterized in terms of their biological activity according to one or more parameters, for example, according to their capacity to induce each of a plurality of cytokines.

The methods of the invention also involve measurement of a test activity of a test composition containing a known TLR ligand. A "test composition" as used herein refers to a composition that includes a test compound and optionally another agent, e.g., a pharmaceutically acceptable carrier and/or another biologically active agent. A test compound can be an immunostimulatory compound or it can be an immunoinhibitory compound. In some aspects of the invention, the test compound is a known TLR ligand. Test compositions of the invention may comprise known TLR agonist or TLR antagonist compounds, generally but not necessarily nominally the same as the reference compositions against which comparison is to be made according to some aspects of the invention. Thus test compositions may encompass immunostimulatory compounds, immunoinhibitory compounds, known TLR ligands, finished pharmaceutical products, and raw materials and other in-process materials used for the preparation of such finished products.

Unlike a reference composition, a test composition is not characterized at all, or is only partially characterized, or is not as well characterized as the reference composition, in terms of its chemical, physical, or (most particularly) biological properties. The methods of the invention permit further characterization of the test composition by comparison with a reference composition. In some aspects, a test composition will be a specific composition previously determined to be a ligand of a specific TLR. In one embodiment the test composition is a representative sample of a particular lot or batch of a specific TLR ligand. In one embodiment the test composition is a representative sample of a particular lot or batch of

a specific TLR ligand formulated for pharmaceutical use, e.g., a sterile solution of the TLR ligand at a determined concentration or activity.

Immunostimulatory and Immunoinhibitory Nucleic Acids

Nucleic acids useful as reference compounds and as test compounds in the methods of the invention include single- and double-stranded natural and synthetic nucleic acids, including those with phosphodiester, stabilized, and chimeric backbones. Also encompassed are at least the following classes of nucleic acids, which are described in detail below: immunostimulatory CpG nucleic acids (CpG nucleic acids), including but not limited to types A, B, and C; immunostimulatory non-CpG nucleic acids, including without limitation methylated CpG nucleic acids, T-rich nucleic acids, TG-motif nucleic acids, CpI motif nucleic acids, and poly-G nucleic acids; and immunoinhibitory nucleic acids. Nucleic acids useful as reference compounds and as test compounds in the methods of the invention also include nucleic acids with modified backbones, including "soft" and "semi-soft" oligonucleotides as described herein. As will be appreciated from the descriptions below, certain of these various classes of nucleic acids can coexist in a given nucleic acid molecule.

A "nucleic acid" as used herein with respect to test compounds and reference compounds used in the methods of the invention, shall refer to any polymer of two or more individual nucleoside or nucleotide units. Typically individual nucleoside or nucleotide units will include any one or combination of deoxyribonucleosides, ribonucleosides, deoxyribonucleotides, and ribonucleotides. The individual nucleotide or nucleoside units of the nucleic acid can be naturally occurring or not naturally occurring. For example, the individual nucleotide units can include deoxyadenosine, deoxycytidine, deoxyguanosine, thymidine, and uracil. In addition to naturally occurring 2'-deoxy and 2'-hydroxyl forms, individual nucleosides also include synthetic nucleosides having modified base moieties and/or modified sugar moieties, e.g., as described in Uhlmann E et al. (1990) *Chem Rev* 90:543-84. The linkages between individual nucleotide or nucleoside units can be naturally occurring or not naturally occurring. For example, the linkages can be phosphodiester, phosphorothioate, phosphorodithioate, phosphoramidate, as well as peptide linkages and other covalent linkages, known in the art, suitable for joining adjacent nucleoside or nucleotide units. The linkages can also be mixed in a single polymer (e.g., a semi-soft backbone). The nucleic acid test compounds and nucleic acid reference compounds typically range in size from 3-4 units to a few tens of units, e.g., 18-40 units.

In some embodiments the nucleic acids are oligonucleotides made up of 2 to about 100 nucleotides, and more typically 4 to about 40 nucleotides. Oligonucleotides composed exclusively of deoxynucleotides are termed oligodeoxyribonucleotides or, equivalently, oligodeoxynucleotides (ODN).

A CpG nucleic acid is an immunostimulatory nucleic acid which contains a cytosine-guanine (CG) dinucleotide, the C residue of which is unmethylated. The effects of CpG nucleic acids on immune modulation have been described extensively in U.S. Pat. Nos. 6,194,388; 6,207,646; 6,214,806; 6,218,371; 6,239,116; and 6,339,068; and published patent applications, such as PCT/US95/01570 (WO 96/02555); PCT/US98/04703 (WO 98/40100); and PCT/US99/09863 (WO 99/56755). The entire contents of each of these patents and published patent applications is hereby incorporated by reference. The entire immunostimulatory nucleic acid can be unmethylated or portions can be unmethylated, but at least the C of the 5'-CG-3' must be unmethylated. The CpG nucleic acid sequences of the invention include, without limitation, those broadly described above as well as those disclosed in U.S. Pat. Nos. 6,207,646 and 6,239,116.

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGTCGTTTTGTCGTT-3' (SEQ ID NO:1).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGACGTTTTGTCGTT-3' (SEQ ID NO:139).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTGTCGTTTTTTTCGA-3' (SEQ ID NO:140).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTCGTCGTTTCGTCGTT-3' (SEQ ID NO:141).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTCGTCGTTTTGTCGTT-3' (SEQ ID NO:142).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTTCGGTCGTTTT-3' (SEQ ID NO:143).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTTCGTGCGTTTTT-3' (SEQ ID NO:144).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTCGTTTTCGGCGGCCGCCG-3' (SEQ ID NO:145).

In one embodiment the CpG nucleic acid has a base sequence provided by 5'-TCGTC_GTTTTAC_GGCGCC_GTGCCG-3' (SEQ ID NO:146).

The oligonucleotides described by SEQ ID NOs: 1, 139-145 are fully stabilized phosphorothioate backbone ODN. The oligonucleotide of SEQ ID NO:146 has a chimeric backbone in which all internucleoside linkages are phosphorothioate except for those indicated by "_", which are phosphodiester.

CpG nucleic acids have been further classified by structure and function into at least the following three types, all of which are intended to be encompassed within the methods of the instant invention: Type B CpG nucleic acids such as SEQ ID NO:1 include the earliest described CpG nucleic acids and characteristically activate B cells but do not induce or only weakly induce expression of IFN-α. Type B nucleic acids are described in U.S. Patents 6,194,388; 6,207,646; 6,214,806; 6,218,371; 6,239,116; and 6,339,068. Type A CpG nucleic acids, described in published international application PCT/US00/26527 (WO 01/22990), incorporate a CpG motif, include a hybrid phosphodiester/phosphorothioate backbone, and characteristically induce plasmacytoid dendritic cells to express large amounts of IFN-α but do not activate or only weakly activate B cells. Type C oligonucleotides incorporate a CpG, include a chimeric backbone, include a GC-rich palindromic or nearly-palindromic region, and are capable of both activating B cells and inducing expression of IFN-α. These have been described, for example, in copending U.S. Pat. application Ser. No. 10/224,523, filed August 19, 2002. Exemplary sequences of A, B and C class nucleic acids are described in the afore-mentioned references, patents and patent applications, the entire contents of which are hereby incorporated by reference herein.

In other embodiments of the invention, a non-CpG nucleic acid is used. A non-CpG nucleic acid is an immunostimulatory nucleic acid which either does not have a CpG motif in its sequence, or has a CpG motif which contains a methylated C residue. In some instances, the non-CpG nucleic acid may still be immunostimulatory by virtue of its having other immunostimulatory motifs such as those described herein and known in the art. In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid. In some instances the non-CpG nucleic acid is still immunostimulatory despite methylation of the C of the CpG motif, even without having another non-CpG immunostimulatory motif described herein and known in the art.

In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-TZGTZGTTTTGTZGTTTTGTZGTT-3' (SEQ ID NO:147), wherein Z represents 5-methylcytosine.

In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-TZGTZGZTGTZTZZGZTTZTTZTTGZZ-3' (SEQ ID NO:148), wherein Z represents 5-methylcytosine.

In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-GZGTTTGZTZTTZTTZTTGZG-3' (SEQ ID NO:149), wherein Z represents 5-methylcytosine.

In one embodiment the non-CpG nucleic acid is a methylated CpG nucleic acid having a base sequence provided by 5'-GZZZAAGZTGGZATZZGTZA-3' (SEQ ID NO:150), wherein Z represents 5-methylcytosine.

Non-CpG nucleic acids include T-rich immunostimulatory nucleic acids. The T-rich immunostimulatory nucleic acids include those disclosed in published PCT patent application PCT/US00/26383 (WO 01/22972), the entire contents of which are incorporated herein by reference. In some embodiments, T-rich nucleic acids 24 bases in length are used. A T-rich nucleic acid is a nucleic acid which includes at least one poly T sequence and/or which has a nucleotide composition of greater than 25% T nucleotide residues. A nucleic acid having a poly-T sequence includes at least four Ts in a row, such as 5'-TTTT-3'. In some embodiments the T-rich nucleic acid includes more than one poly T sequence. In important embodiments, the T-rich nucleic acid may have 2, 3, 4, or more poly T sequences, such as SEQ ID NO:1.

Non-CpG nucleic acids also include poly-G immunostimulatory nucleic acids. A variety of references describe the immunostimulatory properties of poly-G nucleic acids. Pisetsky DS et al. (1993) *Mol Biol Reports* 18:217-221; Krieger M et al. (1994) *Ann Rev Biochem* 63:601-637; Macaya RF et al. (1993) *Proc Natl Acad Sci USA* 90:3745-3749; Wyatt JR et al. (1994) *Proc Natl Acad Sci USA* 91:1356-1360; Rando and Hogan, 1998, In Applied Antisense Oligonucleotide Technology, Krieg and Stein, eds., pp. 335-352; Kimura Y et al. (1994) *J Biochem (Tokyo)* 116:991-994.

The immunostimulatory nucleic acids of the invention can also be those which do not possess CpG, methylated CpG, T-rich, or poly-G motifs.

Exemplary immunostimulatory nucleic acid sequences include but are not limited to those immunostimulatory sequences described and listed in U.S. Non-Provisional Pat. Application No. 09/669,187, filed on September 25, 2000, and in corresponding published PCT patent application PCT/US00/26383 (WO 01/22972).

Immunoinhibitory nucleic acids have been described in Lenert P et al. (2001) *Antisense Nucleic Acid Drug Dev* 11:247-56 and in Stunz L et al. (2002) *Eur J Immunol*

32:1212-22. These inhibitory phosphorothioate ODN (S-ODN) differ from stimulatory S-ODN by having 2-3 G substitutions in the central motif. As inhibitory S-ODN did not directly interfere with the NF-κB DNA binding but prevented CpG-induced NF-κB nuclear translocation of p50, p65, and c-Rel and blocked p105, IκBα, and IκBβ degradation, Lenert et al. suggested that the putative target of immunoinhibitory ODN would lie upstream of inhibitory kinase (IKK) activation. Stunz et al. reported that replacing GCGTT or ACGTT with GCGGG or ACGGG converted a stimulatory 15-mer ODN into an inhibitory ODN. All inhibitory ODN had three consecutive G, and a fourth G increased inhibitory activity, but a deazaguanosine substitution to prevent planar stacking did not affect activity. Inhibitory ODN blocked apoptosis protection and cell-cycle entry induced by stimulatory ODN, but not that induced by lipopolysaccharide, anti-CD40 or anti-IgM+IL-4. ODN-driven up-regulation of cyclin D(2), c-Myc, c-Fos, c-Jun and Bcl(XL) and down-regulation of cyclin kinase inhibitor p27(kip1) were all blocked by inhibitory ODN. Stunz et al. also reported that interference with uptake of stimulatory ODN did not account for the inhibitory effects of the immunoinhibitory nucleic acids.

In one embodiment the immunoinhibitory nucleic acid has a base sequence provided by 5'-TCCTGGCGGGGAAGT-3' (SEQ ID NO:151).

Immunoinhibitory nucleic acids have also been described in U.S. Pat. No. 6,194,388, issued to Krieg et al. The immunoinhibitory oligonucleotides disclosed by Krieg et al. are oligonucleotides with GCG trinucleotides at or near the ends of the oligonucleotide and are represented by the formula $5'\,GCGX_nGCG\,3'$ in which X is a nucleotide and n is an integer between 0 and 50.

The nucleic acids used as either test or reference compounds can be double-stranded or single-stranded. They can be deoxyribonucleotide (DNA) or ribonucleotide (RNA) molecules. Generally, double-stranded molecules are more stable in vivo, while single-stranded molecules have increased immune activity. Thus in some the nucleic acid is single-stranded and in other embodiments the nucleic acid is double-stranded. In certain embodiments, while the nucleic acid is single-stranded, it is capable of forming secondary and tertiary structures (e.g., by folding back on itself, or by hybridizing with itself either throughout its entirety or at select segments along its length). Accordingly, while the primary structure of such a nucleic acid may be single-stranded, its higher order structures may be double- or triple-stranded.

For facilitating uptake into cells, the nucleic acids are preferably in the range of 6 to 100 bases in length. However, nucleic acids of any size equal to or greater than 6 nucleotides (even many kb long) are capable of inducing an immune response. Preferably the nucleic acid is in the range of between 8 and 100 and in some embodiments between 8 and 50 or 8 and 30 nucleotides in size.

The terms "nucleic acid" and "oligonucleotide" are used interchangeably to mean multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)). As used herein, the terms "nucleic acid" and "oligonucleotide" refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms "nucleic acid" and "oligonucleotide" shall also include polynucleosides (i.e., a polynucleotide minus the phosphate) and any other organic base containing polymer. Nucleic acid molecules can be obtained from existing nucleic acid sources (e.g., genomic or cDNA), but are preferably synthetic (e.g., produced by nucleic acid synthesis).

The terms "nucleic acid" and "oligonucleotide" also encompass nucleic acids or oligonucleotides with substitutions or modifications, such as in the bases and/or sugars. For example, they include nucleic acids having backbone sugars that are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 2' position and other than a phosphate group or hydroxy group at the 5' position. Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition, modified nucleic acids may include sugars such as arabinose or 2'-fluoroarabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have an amino acid backbone with nucleic acid bases). Other examples are described in more detail below.

The immunostimulatory and immunoinhibitory nucleic acids can encompass various chemical modifications and substitutions, in comparison to natural RNA and DNA, involving a phosphodiester internucleoside bridge, a β-D-ribose unit and/or a natural nucleoside base (adenine, guanine, cytosine, thymine, uracil). Examples of chemical modifications are known to the skilled person and are described, for example, in Uhlmann E et al. (1990) *Chem Rev* 90:543; "Protocols for Oligonucleotides and Analogs" Synthesis and Properties & Synthesis and Analytical Techniques, S. Agrawal, Ed, Humana Press, Totowa, USA 1993; Crooke ST et al. (1996) *Annu Rev Pharmacol Toxicol* 36:107-129; and Hunziker J et al. (1995) *Mod Synth*

Methods 7:331-417. An oligonucleotide according to the invention may have one or more modifications, wherein each modification is located at a particular phosphodiester internucleoside bridge and/or at a particular β-D-ribose unit and/or at a particular natural nucleoside base position in comparison to an oligonucleotide of the same sequence which is composed of natural DNA or RNA.

For example, the oligonucleotides may comprise one or more modifications and wherein each modification is independently selected from:

a) the replacement of a phosphodiester internucleoside bridge located at the 3' and/or the 5' end of a nucleoside by a modified internucleoside bridge,

b) the replacement of phosphodiester bridge located at the 3' and/or the 5' end of a nucleoside by a dephospho bridge,

c) the replacement of a sugar phosphate unit from the sugar phosphate backbone by another unit,

d) the replacement of a β-D-ribose unit by a modified sugar unit, and

e) the replacement of a natural nucleoside base by a modified nucleoside base.

More detailed examples for the chemical modification of an oligonucleotide are as follows.

The oligonucleotides may include modified internucleotide linkages, such as those described in (a) or (b) above. These modified linkages may be partially resistant to degradation (e.g., are stabilized). A "stabilized oligonucleotide molecule" shall mean an oligonucleotide that is relatively resistant to *in vivo* degradation (e.g., via an exo- or endo-nuclease) resulting from such modifications. Oligonucleotides having phosphorothioate linkages, in some embodiments, may provide maximal activity and protect the oligonucleotide from degradation by intracellular exo- and endo-nucleases.

A phosphodiester internucleoside bridge located at the 3' and/or the 5' end of a nucleoside can be replaced by a modified internucleoside bridge, wherein the modified internucleoside bridge is for example selected from phosphorothioate, phosphorodithioate, NR^1R^2-phosphoramidate, boranophosphate, α-hydroxybenzyl phosphonate, phosphate-(C_1-C_{21})-O-alkyl ester, phosphate-[(C_6-C_{12})aryl-(C_1-C_{21})-O-alkyl]ester, (C_1-C_8)alkylphosphonate and/or (C_6-C_{12})arylphosphonate bridges, (C_7-C_{12})-α-hydroxymethyl-aryl (e.g., disclosed in WO 95/01363), wherein (C_6-C_{12})aryl, (C_6-C_{20})aryl and (C_6-C_{14})aryl are optionally substituted by halogen, alkyl, alkoxy, nitro, cyano, and where R^1 and R^2 are, independently of each other, hydrogen, (C_1-C_{18})-alkyl, (C_6-C_{20})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl, preferably hydrogen,

$(C_1\text{-}C_8)$-alkyl, preferably $(C_1\text{-}C_4)$-alkyl and/or methoxyethyl, or R^1 and R^2 form, together with the nitrogen atom carrying them, a 5-6-membered heterocyclic ring which can additionally contain a further heteroatom from the group O, S and N.

The replacement of a phosphodiester bridge located at the 3' and/or the 5' end of a nucleoside by a dephospho bridge (dephospho bridges are described, for example, in Uhlmann E and Peyman A in "Methods in Molecular Biology", Vol. 20, "Protocols for Oligonucleotides and Analogs", S. Agrawal, Ed., Humana Press, Totowa, 1993, Chapter 16, pp. 355 ff), wherein a dephospho bridge is for example selected from the dephospho bridges formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethyl-hydrazo, dimethylenesulfone and/or silyl groups.

A sugar phosphate unit (i.e., a β-D-ribose and phosphodiester internucleoside bridge together forming a sugar phosphate unit) from the sugar phosphate backbone (i.e., a sugar phosphate backbone is composed of sugar phosphate units) can be replaced by another unit, wherein the other unit is for example suitable to build up a "morpholino-derivative" oligomer (as described, for example, in Stirchak EP et al. (1989) *Nucleic Acids Re*s 17:6129-41), that is, e.g., the replacement by a morpholino-derivative unit; or to build up a polyamide nucleic acid ("PNA"; as described for example, in Nielsen PE et al. (1994) *Bioconjug Chem* 5:3-7), that is, e.g., the replacement by a PNA backbone unit, e.g., by 2-aminoethylglycine. The oligonucleotide may have other carbohydrate backbone modifications and replacements, such as peptide nucleic acids with phosphate groups (PHONA), locked nucleic acids (LNA), and oligonucleotides having backbone sections with alkyl linkers or amino linkers. The alkyl linker may be branched or unbranched, substituted or unsubstituted, and chirally pure or a racemic mixture.

A β-ribose unit or a β-D-2'-deoxyribose unit can be replaced by a modified sugar unit, wherein the modified sugar unit is for example selected from β-D-ribose, α-D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-F-arabinose, 2'-O-$(C_1\text{-}C_6)$alkyl-ribose, preferably 2'-O-$(C_1\text{-}C_6)$alkyl-ribose is 2'-O-methylribose, 2'-O-$(C_2\text{-}C_6)$alkenyl-ribose, 2'-[O-$(C_1\text{-}C_6)$alkyl-O-$(C_1\text{-}C_6)$alkyl]-ribose, 2'-NH_2-2'-deoxyribose, β-D-xylo-furanose, α-arabinofuranose, 2,4-dideoxy-β-D-erythro-hexo-pyranose, and carbocyclic (described, for example, in Froehler J (1992) *Am Chem Soc* 114:8320) and/or open-chain sugar analogs (described, for example, in Vandendriessche et al. (1993) *Tetrahedron* 49:7223) and/or bicyclosugar analogs (described, for example, in Tarkov M et al. (1993) *Helv Chim Acta* 76:481).

In some embodiments the sugar is 2'-O-methylribose, particularly for one or both nucleotides linked by a phosphodiester or phosphodiester-like internucleoside linkage.

In some embodiments, the nucleic acids may be soft or semi-soft nucleic acids. A soft nucleic acid is an immunostimulatory nucleic acid having a partially stabilized backbone, in which phosphodiester or phosphodiester-like internucleotide linkages occur only within and immediately adjacent to at least one internal pyrimidine -purine dinucleotide (YZ). Preferably YZ is YG, a pyrimidine-guanosine (YG) dinucleotide. The at least one internal YZ dinucleotide itself has a phosphodiester or phosphodiester-like internucleotide linkage. A phosphodiester or phosphodiester-like internucleotide linkage occurring immediately adjacent to the at least one internal YZ dinucleotide can be 5', 3', or both 5' and 3' to the at least one internal YZ dinucleotide.

In particular, phosphodiester or phosphodiester-like internucleotide linkages involve "internal dinucleotides". An internal dinucleotide in general shall mean any pair of adjacent nucleotides connected by an internucleotide linkage, in which neither nucleotide in the pair of nucleotides is a terminal nucleotide, i.e., neither nucleotide in the pair of nucleotides is a nucleotide defining the 5' or 3' end of the nucleic acid. Thus a linear nucleic acid that is n nucleotides long has a total of n-1 dinucleotides and only n-3 internal dinucleotides. Each internucleotide linkage in an internal dinucleotide is an internal internucleotide linkage. Thus a linear nucleic acid that is n nucleotides long has a total of n-1 internucleotide linkages and only n-3 internal internucleotide linkages. The strategically placed phosphodiester or phosphodiester-like internucleotide linkages, therefore, refer to phosphodiester or phosphodiester-like internucleotide linkages positioned between any pair of nucleotides in the nucleic acid sequence. In some embodiments the phosphodiester or phosphodiester-like internucleotide linkages are not positioned between either pair of nucleotides closest to the 5' or 3' end.

Preferably a phosphodiester or phosphodiester-like internucleotide linkage occurring immediately adjacent to the at least one internal YZ dinucleotide is itself an internal internucleotide linkage. Thus for a sequence N_1 YZ N_2, wherein N_1 and N_2 are each, independent of the other, any single nucleotide, the YZ dinucleotide has a phosphodiester or phosphodiester-like internucleotide linkage, and in addition (a) N_1 and Y are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N_1 is an internal nucleotide, (b) Z and N_2 are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N_2 is an internal nucleotide, or (c) N_1 and Y are linked by a phosphodiester or

phosphodiester-like internucleotide linkage when N_1 is an internal nucleotide and Z and N_2 are linked by a phosphodiester or phosphodiester-like internucleotide linkage when N_2 is an internal nucleotide.

Soft nucleic acids according to the instant invention are believed to be relatively susceptible to nuclease cleavage compared to completely stabilized nucleic acids. Without meaning to be bound to a particular theory or mechanism, it is believed that soft nucleic acids of the invention are cleavable to fragments with reduced or no immunostimulatory activity relative to full-length soft nucleic acids. Incorporation of at least one nuclease-sensitive internucleotide linkage, particularly near the middle of the nucleic acid, is believed to provide an "off switch" which alters the pharmacokinetics of the nucleic acid so as to reduce the duration of maximal immunostimulatory activity of the nucleic acid. This can be of particular value in tissues and in clinical applications in which it is desirable to avoid injury related to chronic local inflammation or immunostimulation, e.g., the kidney.

A semi-soft nucleic acid is an immunostimulatory nucleic acid having a partially stabilized backbone, in which phosphodiester or phosphodiester-like internucleotide linkages occur only within at least one internal pyrimidine-purine (YZ) dinucleotide. Semi-soft nucleic acids generally possess increased immunostimulatory potency relative to corresponding fully stabilized immunostimulatory nucleic acids. Due to the greater potency of semi-soft nucleic acids, semi-soft nucleic acids may be used, in some instances, at lower effective concentations and have lower effective doses than conventional fully stabilized immunostimulatory nucleic acids in order to achieve a desired biological effect.

It is believed that the foregoing properties of semi-soft nucleic acids generally increase with increasing "dose" of phosphodiester or phosphodiester-like internucleotide linkages involving internal YZ dinucleotides. Thus it is believed, for example, that generally for a given nucleic acid sequence with five internal YZ dinucleotides, an nucleic acid with five internal phosphodiester or phosphodiester-like YZ internucleotide linkages is more immunostimulatory than an nucleic acid with four internal phosphodiester or phosphodiester-like YG internucleotide linkages, which in turn is more immunostimulatory than an nucleic acid with three internal phosphodiester or phosphodiester-like YZ internucleotide linkages, which in turn is more immunostimulatory than an nucleic acid with two internal phosphodiester or phosphodiester-like YZ internucleotide linkages, which in turn is more immunostimulatory than an nucleic acid with one internal phosphodiester or phosphodiester-like YZ internucleotide linkage. Importantly, inclusion of even one internal phosphodiester or

phosphodiester-like YZ internucleotide linkage is believed to be advantageous over no internal phosphodiester or phosphodiester-like YZ internucleotide linkage. In addition to the number of phosphodiester or phosphodiester-like internucleotide linkages, the position along the length of the nucleic acid can also affect potency.

The soft and semi-soft nucleic acids will generally include, in addition to the phosphodiester or phosphodiester-like internucleotide linkages at preferred internal positions, 5' and 3' ends that are resistant to degradation. Such degradation-resistant ends can involve any suitable modification that results in an increased resistance against exonuclease digestion over corresponding unmodified ends. For instance, the 5' and 3' ends can be stabilized by the inclusion thereof at least one phosphate modification of the backbone. In a preferred embodiment, the at least one phosphate modification of the backbone at each end is independently a phosphorothioate, phosphorodithioate, methylphosphonate, or methylphosphorothioate internucleotide linkage. In another embodiment, the degradation-resistant end includes one or more nucleotide units connected by peptide or amide linkages at the 3' end.

A phosphodiester internucleotide linkage is the type of linkage characteristic of nucleic acids found in nature. The phosphodiester internucleotide linkage includes a phosphorus atom flanked by two bridging oxygen atoms and bound also by two additional oxygen atoms, one charged and the other uncharged. Phosphodiester internucleotide linkage is particularly preferred when it is important to reduce the tissue half-life of the nucleic acid.

A phosphodiester-like internucleotide linkage is a phosphorus-containing bridging group that is chemically and/or diastereomerically similar to phosphodiester. Measures of similarity to phosphodiester include susceptibility to nuclease digestion and ability to activate RNAse H. Thus for example phosphodiester, but not phosphorothioate, nucleic acids are susceptible to nuclease digestion, while both phosphodiester and phosphorothioate nucleic acids activate RNAse H. In a preferred embodiment the phosphodiester-like internucleotide linkage is boranophosphate (or equivalently, boranophosphonate) linkage. U.S. Patent No. 5,177,198; U.S. Patent No. 5,859,231; U.S. Patent No. 6,160,109; U.S. Patent No. 6,207,819; Sergueev et al., (1998) *J Am Chem Soc* 120:9417-27. In another preferred embodiment the phosphodiester-like internucleotide linkage is diasteromerically pure Rp phosphorothioate. It is believed that diasteromerically pure Rp phosphorothioate is more susceptible to nuclease digestion and is better at activating RNAse H than mixed or diastereomerically pure Sp phosphorothioate. Stereoisomers of CpG nucleic acids are the subject of co-pending U.S.

patent application 09/361,575 filed July 27, 1999, and published PCT application PCT/US99/17100 (WO 00/06588). It is to be noted that for purposes of the instant invention, the term "phosphodiester-like internucleotide linkage" specifically excludes phosphorodithioate and methylphosphonate internucleotide linkages.

As described above the soft and semi-soft nucleic acids of the invention may have phosphodiester like linkages between C and G. One example of a phosphodiester-like linkage is a phosphorothioate linkage in an Rp conformation. Nucleic acid p-chirality can have apparently opposite effects on the immune activity of a CpG nucleic acid, depending upon the time point at which activity is measured. At an early time point of 40 minutes, the R_p but not the S_P stereoisomer of phosphorothioate CpG nucleic acid induces JNK phosphorylation in mouse spleen cells. In contrast, when assayed at a late time point of 44 hr, the S_P but not the R_p stereoisomer is active in stimulating spleen cell proliferation. This difference in the kinetics and bioactivity of the R_p and S_P stereoisomers does not result from any difference in cell uptake, but rather most likely is due to two opposing biologic roles of the p-chirality. First, the enhanced activity of the Rp stereoisomer compared to the Sp for stimulating immune cells at early time points indicates that the Rp may be more effective at interacting with the CpG receptor, TLR9, or inducing the downstream signaling pathways. On the other hand, the faster degradation of the Rp PS-nucleic acids compared to the Sp results in a much shorter duration of signaling, so that the Sp PS-nucleic acids appear to be more biologically active when tested at later time points.

A surprisingly strong effect is achieved by the p-chirality at the CpG dinucleotide itself. In comparison to a stereo-random CpG nucleic acid the congener in which the single CpG dinucleotide was linked in Rp was slightly more active, while the congener containing an Sp linkage was nearly inactive for inducing spleen cell proliferation.

Nucleic acids also include substituted purines and pyrimidines such as C-5 propyne pyrimidine and 7-deaza-7-substituted purine modified bases. Wagner RW et al. (1996) *Nat Biotechnol* 14:840-4. Purines and pyrimidines include but are not limited to adenine, cytosine, guanine, and thymine, and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted aromatic moieties.

A modified base is any base which is chemically distinct from the naturally occurring bases typically found in DNA and RNA such as T, C, G, A, and U, but which share basic chemical structures with these naturally occurring bases. The modified nucleoside base may be, for example, selected from hypoxanthine, uracil, dihydrouracil, pseudouracil, 2-thiouracil,

4-thiouracil, 5-aminouracil, 5-(C_1-C_6)-alkyluracil, 5-(C_2-C_6)-alkenyluracil, 5-(C_2-C_6)-alkynyluracil, 5-(hydroxymethyl)uracil, 5-chlorouracil, 5-fluorouracil, 5-bromouracil, 5-hydroxycytosine, 5-(C_1-C_6)-alkylcytosine, 5-(C_2-C_6)-alkenylcytosine, 5-(C_2-C_6)-alkynylcytosine, 5-chlorocytosine, 5-fluorocytosine, 5-bromocytosine, N^2-dimethylguanine, 2,4-diamino-purine, 8-azapurine, a substituted 7-deazapurine, preferably 7-deaza-7-substituted and/or 7-deaza-8-substituted purine, 5-hydroxymethylcytosine, N4-alkylcytosine, e.g., N4-ethylcytosine, 5-hydroxydeoxycytidine, 5-hydroxymethyldeoxycytidine, N4-alkyldeoxycytidine, e.g., N4-ethyldeoxycytidine, 6-thiodeoxyguanosine, and deoxyribonucleosides of nitropyrrole, C5-propynylpyrimidine, and diaminopurine e.g., 2,6-diaminopurine, inosine, 5-methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, hypoxanthine or other modifications of a natural nucleoside bases. This list is meant to be exemplary and is not to be interpreted to be limiting.

Modified cytosines include but are not limited to 5-substituted cytosines (e.g., 5-methyl-cytosine, 5-fluoro-cytosine, 5-chloro-cytosine, 5-bromo-cytosine, 5-iodo-cytosine, 5-hydroxy-cytosine, 5-hydroxymethyl-cytosine, 5-difluoromethyl-cytosine, and unsubstituted or substituted 5-alkynyl-cytosine), 6-substituted cytosines, N4-substituted cytosines (e.g., N4-ethyl-cytosine), 5-aza-cytosine, 2-mercapto-cytosine, isocytosine, pseudo-isocytosine, cytosine analogs with condensed ring systems (e.g., N,N'-propylene cytosine or phenoxazine), and uracil and its derivatives (e.g., 5-fluoro-uracil, 5-bromo-uracil, 5-bromovinyl-uracil, 4-thio-uracil, 5-hydroxy-uracil, 5-propynyl-uracil). In another embodiment, the cytosine base is substituted by a universal base (e.g., 3-nitropyrrole, P-base), an aromatic ring system (e.g., fluorobenzene or difluorobenzene) or a hydrogen atom (dSpacer).

Modified guanines include but are not limited to 7-deazaguanine, 7-deaza-7-substituted guanine (such as 7-deaza-7-(C2-C6)alkynylguanine), 7-deaza-8-substituted guanine, hypoxanthine, N2-substituted guanines (e.g., N2-methyl-guanine), 5-amino-3-methyl-3H,6H-thiazolo[4,5-d]pyrimidine-2,7-dione, 2,6-diaminopurine, 2-aminopurine, purine, indole, adenine, substituted adenines (e.g., N6-methyl-adenine, 8-oxo-adenine) 8-substituted guanine (e.g., 8-hydroxyguanine and 8-bromoguanine), and 6-thioguanine. In another embodiment, the guanine base is substituted by a universal base (e.g., 4-methyl-indole, 5-nitro-indole, and K-base), an aromatic ring system (e.g., benzimidazole or dichloro-benzimidazole, 1-methyl-1H-[1,2,4]triazole-3-carboxylic acid amide) or a hydrogen atom (dSpacer).

For use in the instant invention, the oligonucleotide reference compounds and test compounds can be synthesized *de novo* using any of a number of procedures well known in the art, for example, the β-cyanoethyl phosphoramidite method (Beaucage SL et al. (1981) *Tetrahedron Lett* 22:1859), or the nucleoside H-phosphonate method (Garegg et al. (1986) *Tetrahedron Lett* 27:4051-4; Froehler BC et al. (1986) *Nucleic Acids Res* 14:5399-407; Garegg et al (1986) *Tetrahedron Lett* 27:4055-8; Gaffney et al. (1988) *Tetrahedron Lett* 29:2619-22). These chemistries can be performed by a variety of automated nucleic acid synthesizers available in the market. These oligonucleotides are referred to as synthetic oligonucleotides. An isolated oligonucleotide generally refers to an oligonucleotide which is separated from components which it is normally associated with in nature. As an example, an isolated oligonucleotide may be one which is separated from a cell, from a nucleus, from mitochondria or from chromatin.

Modified backbones such as phosphorothioates can be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl-and alkyl-phosphonates can be made, e.g., as described in U.S. Pat. No. 4,469,863; and alkylphosphotriesters (in which the charged oxygen moiety is alkylated as described in U.S. Pat. No. 5,023,243 and European Pat. No. 092,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described (e.g., Uhlmann E et al. (1990) *Chem Rev* 90:544; Goodchild J (1990) *Bioconjugate Chem* 1:165).

TLR expression

The cell lines can be used in their native state without any modification. For example, in the case of the RPMI 8226 cell line, it can be used to identify compounds that signal through at least TLR9 and/or TLR7. In other instances, however, the cell line can be modified to express a TLR that it does not naturally express. In still other instances, the cell to be used in the screening method may express one or more endogenous TLR and yet still be manipulated to express an additional TLR different from those it endogenously expresses. The cell may also be manipulated in order to increase or decrease the level of TLR that it endogenously expresses. The cells may be stably or transiently transfected.

A cell that does not naturally express a protein or polypeptide, but is genetically manipulated to do so is referred to as ectopically expressing the protein or polypeptide.

The basic screening method remains the same regardless of which TLR is expressed by the cell. However, the reference compound and the readout may vary depending upon the TLR(s) expressed. In the most simple aspect, the screening method is used to identify a compound that signals through a TLR such as for example TLR9. In this case, the positive reference compound may be an immunostimulatory compound already known to act through TLR9 (e.g., CpG nucleic acid).

The methods of the invention involve, in part, contacting a functional TLR with a test composition. A functional TLR is a full-length TLR protein or a fragment thereof capable of inducing or inhibiting a signal in response to interaction with its ligand. Generally the functional TLR will include at least a TLR ligand-binding fragment of the extracellular domain of the full-length TLR and at least a fragment of a TIR domain capable of interacting with another Toll homology domain-containing polypeptide, e.g., MyD88. In various embodiments the functional TLR is a full-length TLR selected from TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, and TLR10.

To date, there are eleven TLRs known. Nucleic acid and amino acid sequences for ten currently known human TLRs are available from public databases such as GenBank. Similarly, nucleic acid and amino acid sequences for various TLRs from numerous non-human species are also available from public databases including GenBank. For example, nucleic acid and amino acid sequences for human TLR9 (hTLR9) can be found as GenBank accession numbers AF245704 (coding region spanning nucleotides 145-3243) (SEQ ID NO: 60) and AAF78037 (SEQ ID NO: 62), respectively. Nucleic acid and amino acid sequences for murine TLR9 (mTLR9) can be found as GenBank accession numbers AF348140 (coding region spanning nucleotides 40-3138) (SEQ ID NO: 68) and AAK29625 (SEQ ID NO: 72), respectively.

Nucleic acid and amino acid sequences for human TLR8 (hTLR8) can be found as GenBank accession numbers AF245703 (coding region spanning nucleotides 49-3174) (SEQ ID NO: 46) and AAF78036 (SEQ ID NO: 50), respectively. Nucleic acid and amino acid sequences for murine TLR8 (mTLR8) can be found as GenBank accession numbers AY035890 (coding region spanning nucleotides 59-3157) (SEQ ID NO: 55) and AAK62677 (SEQ ID NO: 57), respectively.

Nucleic acid and amino acid sequences for human TLR7 (hTLR7) can be found as GenBank accession numbers AF240467 (coding region spanning nucleotides 135-3285) (SEQ ID NO: 31) and AAF60188 (SEQ ID NO: 34), respectively. Nucleic acid and amino acid

sequences for murine TLR7 (mTLR7) can be found as GenBank accession numbers AY035889 (coding region spanning nucleotides 49-3201) (SEQ ID NO: 38) and AAK62676 (SEQ ID NO: 41), respectively.

Nucleic acid and amino acid sequences for human TLR3 (hTLR3) can be found as GenBank accession numbers NM_003265 (coding region spanning nucleotides 102-2816) (SEQ ID NO: 7) and NP_003256 (SEQ ID NO: 8), respectively. Nucleic acid and amino acid sequences for murine TLR3 (hTLR3) can be found as GenBank accession numbers AF355152 (coding region spanning nucleotides 44-2761) (SEQ ID NO: 9) and AAK26117 (SEQ ID NO: 10), respectively.

Nucleic acid and amino acid sequences for human TLR1 (hTLR1) can be found as GenBank accession numbers NM_003263 and NP_003254, respectively. Nucleic acid and amino acid sequences for murine TLR1 (mTLR1) can be found as GenBank accession numbers NM_030682 and NP_109607, respectively.

The functional TLR also is not limited to native TLR polypeptides. As used herein, a native TLR is one that is naturally occurring. The TLR may be a non-native (or non-naturally occurring TLR). An example is a chimeric TLR having an extracellular domain and the cytoplasmic domain derived from TLRs from different species. Such chimeric TLR polypeptides can include, for example, a human TLR extracellular domain and a murine TLR cytoplasmic domain. In alternative embodiments, such chimeric TLR polypeptides can include chimerae created with different TLR splice variants or allotypes.

TLR Signaling Pathways

The screening methods provided by the invention measure TLR signaling activity. TLR signaling activity is activity that results from interaction of a TLR with a TLR ligand. TLR signaling can be measured in a number of ways including but not limited to interaction between a TLR and a protein or factor (such as an adaptor protein), interaction between downstream proteins or factors (such as an adaptor protein) with each other, activation of nuclear factors such as transcription factors or transcription complexes, up- or down-regulation of genes, phosphorylation or dephosphorylation of proteins or factors in the signaling cascade, expression, production and/or secretion of cytokines and/or chemokines, changes in cell cycle status, up- or down-regulation of cell surface marker expression, and the like. Those of ordinary skill in the art are familiar with assays for measuring these latter

events including but not limited to gel shift assays, immunoprecipitations, phosphorylation status analysis of proteins, Northern analysis, RT-PCR analysis, etc.

The following is an exemplary TLR signaling pathway or cascade. It is to be understood that this is meant to be illustrative and that different factors may be involved in the signaling of particular TLR. One TLR signaling pathway is known to use the cytoplasmic Toll/IL-1 receptor (TIR) homology domain, present in all TLRs. This domain interacts (e.g., binds to) and thereby transduces a signal to a similar domain on an adapter protein (e.g., MyD88). This type of interaction is referred to as a like:like interaction of TIR domains. This interaction is followed by an another interaction between the adapter protein and a kinase, through their respective "death domains". In the case of at least TLR4 signaling, the kinase then interacts with tumor necrosis factor (TNF) receptor-associated factor-6 (TRAF6). Medzhitov R et al., *Mol Cell* 2:253 (1998); Kopp EB et al., *Curr Opin Immunol* 11:15 (1999). After TRAF6, two sequential kinase activation steps lead to phosphorylation of the inhibitory protein I kappa B and its dissociation from NF-κB. The first kinase is a mitogen-activated kinase kinase kinase (MAPKKK) known as NIK, for NF-κB-inducing kinase. The target of this kinase is another kinase made up of two chains, called I kappa B kinase α (IKK α) and I kappa B kinase β (IKK β), that together form a heterodimer of IKKα:IKKβ, which phosphorylates I kappa B. NF-κB translocates to the nucleus to activate genes with kappa B binding sites in their promoters and enhancers such as the genes encoding IL-6, IL-8, the p40 subunit of IL-12, and the costimulatory molecule CD86. The signaling mechanisms of TLRs are not limited to this pathway; other signaling pathways exist and can be used in the screening readouts of the methods provided herein.

The screening assays employ a number of readouts (or parameters). The readouts can be native readouts. A native readout is one that does not rely on introduction of a reporter construct into the cell of interest. The readouts can be artificial. An artificial readout is one that relies on introduction of a reporter construct into the cell of interest. Examples of both are provided herein. In still other embodiments, a given assay may measure one or more native readouts and one or more artificial readouts. Each readout whether native or artificial is related to signaling pathways that ensue after TLR engagement with a ligand.

Each cell line described herein will be associated with a particular set of native readouts which the invention seeks to determine in the screening assays provided. As an example, the response of the RPMI 8226 cell line to an immunomodulatory molecule can be assessed in terms of native readouts such as CD71 expression, CD86 expression, HLA-DR

expression, IL-8 expression, IL-8 production, IL-8 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF-α expression, TNF-α production and TNF-α secretion. RAMOS response can be assessed, inter alia, by CD80 cell surface expression. Raji response can be assessed, inter alia, by IL-6 secretion.

As described in greater detail herein, the cell line can be used in an unmodified form. In one respect, an unmodified cell line will naturally respond to a TLR ligand through a native readout system. For example, an RPMI 8226 cell exposed to an immunostimulatory TLR ligand may increase expression of IP-10 from the native gene locus. Alternatively, the cell line may be modified to contain a reporter construct that acts as a surrogate for the IP-10 gene locus. For example, the reporter construct may contain the TLR responsive promoter elements that are naturally found in the native IP-10 locus operably linked to a reporter coding sequence that encodes a gene product that is detectable and quantifiable. The structure and variability of suitable reporter constructs will be discussed in greater detail herein.

Readouts typically include the induction of a gene under control of a specific promoter such as a NF-κB promoter. The gene under the control of the NF-κB promoter can be a gene which naturally includes an NF-κB promoter or it can be a gene in a construct in which an NF-κB promoter has been inserted. Endogenous genes and transfected constructs which include the NF-κB promoter include but are not limited to IL-8, IL-12 p40, NF-κB-luc, IL-12 p40-luc, and TNF-luc.

Increases in cytokine levels can result from increased production, increased stability, increased secretion, or any combination of the forgoing, of the cytokine in response to the TLR-mediated signaling. Cytokines generally include, without limitation, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-11, IL-12, IL-13, IL-15, IL-18, IFN-α, IFN-β, IFN-γ, TNF-α, GM-CSF, G-CSF, M-CSF. Th1 cytokines include but are not limited to IL-2, IFN-γ, and IL-12. Th2 cytokines include but are not limited to IL-4, IL-5, and IL-10.

Increases in chemokine levels can result from increased production, increased stability, increased secretion, or any combination of the forgoing, of the chemokine in response to the TLR-mediated signaling. Chemokines of particular significance in the invention include but are not limited to CCL5 (RANTES), CXCL9 (Mig), CXCL10 (IP-10), CXCL11 (I-TAC), IL-8, and MCP-1.

TLR signaling activity can also be measured by phosphorylation, such as total cellular phosphorylation or phosphorylation of specific factors such as but not limited to IRAK, ERK, MyD88, TRAF6, p38, NF-κB subunits, c-Jun and c-Fos.

TLR signaling activity can be measured by changes in gene expression. The expression of CD71, CD86, CD80, CD69, CD54, HLA-DR, HLA class I, IL-6, IL-8, IL-10, IP-9, IP-10, IFN-α, TNF-α, and the like can be assessed as a measure of TLR signaling activity. Gene expression analysis may be performed using microarray techniques.

TLR signaling activity can also be measured by cell proliferation status or changes thereto.

TLR signaling activity can also be measured by cell surface marker expression such as the cell surface expression of markers such as but not limited to CD71, CD86, HLA-DR, CD80, HLA class I, CD54 and CD69.

TLR signaling activity can also be measured by antibody secretion such as but not limited to IgM secretion.

Reporter and Expression Constructs

The cells can be manipulated by the introduction of expression and/or reporter constructs. The expression constructs preferably comprise a TLR coding sequence, as described above. The reporter constructs can be used as surrogate measures of native TLR signaling activity. These reporter constructs are intended to substitute for the "native" readouts capable with the cell line. In order to act as substitutes, the reporter constructs include a promoter element derived from a gene known to be modulated following TLR engagement with a TLR ligand. The reporter construct further includes a coding sequence linked to the promoter. The coding sequence is usually that of a reporter (i.e., a protein that is detectable or quantifiable).

The reporter construct generally includes a promoter, a coding sequence and a polyadenylation signal. These nucleic acids shall include, as necessary, 5' non-transcribing and 5' non-translating sequences involved with the initiation of transcription and translation, respectively, such as a TATA box, capping sequence, CAAT sequence, in addition to promoter elements that are responsive to TLR signaling. The nucleic acid constructs may optionally include enhancer sequences or upstream activator sequences as desired.

The promoter in the reporter construct will include a TLR responsive promoter element, and will therefore be regarded as a TLR responsive promoter. As used herein, a

TLR responsive promoter is a promoter having an activity that is modulated (i.e., either activated or inhibited) by signaling through a TLR (e.g., by TLR interaction with its ligand). In order to be modulated by TLR signaling, the promoter contains sites that are bound by transcription factors modulated by TLR signaling. The factors may be activated or inhibited by TLR signaling. Activation of the transcription factor includes increases in the activity of the transcription factor per se, increases in its ability to interact with other factors or with DNA that serve to increase its activity, and increases in its transcription and translation (i.e., increased mRNA and protein levels of the transcription factor). Conversely, inhibition of the transcription factor includes decreases in the activity of the transcription factor per se, decreases in its ability to interact with other factors or with DNA that serve to decrease its activity, and decreases in its transcription and translation (i.e., decreased mRNA and protein levels of the transcription factor). The effect on the transcription factor is usually the downstream result of other interactions in the signaling pathway. The expression of coding sequences linked to such promoters will therefore be modulated by TLR signaling events, and it is the level of expression of these coding sequences that can be used as a readout of TLR signaling in the screening methods provided herein.

The TLR responsive promoter may comprise a transcription factor binding site selected from the group consisting of a NF-κB binding site, an AP-1 binding site, a CRE, a SRE, an interferon-stimulated response element (ISRE), a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE, among others. These binding sites and their sequences are known in the art. Below is a exemplary list of these sequences.

W = A or T, R = A or G, Y = C or T

NF-κB Binding site:

Consensus p50 subunit
5' GGGGATYCCC 3' (SEQ ID NO:90)

Consensus p65 subunit
5' GGGRNTTTCC 3' (SEQ ID NO:91)

Example of p65 subunit binding site
5' AGT TGA GGG GAC TTT CCC AGG C 3' (SEQ ID NO:92)

CREB Binding site:
5'AGA GAT TGC CTG ACG TCA GAG AGC TAG 3' (SEQ ID NO:93)

AP-1 Binding site:

5'- CGC TTG ATG AGT CAG CCG GAA –3' (SEQ ID NO:94)
5'- CGC ATG AGT CAG ACA –3' (SEQ ID NO:95)

ISRE :

5'- TGCAGAAGTGAAACTGAGG-3' (SEQ ID NO:96)
5'- AGAACGAAACA-3' (SEQ ID NO:97)
5'- GAGAAGTGAAAGTGG-3' (SEQ ID NO:98)
5'- TAAGAACATGAAACTGAA-3' (SEQ ID NO:99)
5'- ATGAAACTGAAAGTA-3' (SEQ ID NO:100)
5'- TGAAAACCGAAAGCGC-3' (SEQ ID NO:101)
5'- AGAAATGGAAAGT-3' (SEQ ID NO:102)

SRE

5'- TCACCCCAC-3' (SEQ ID NO:103)
5'- CTCACCCCAC-3' (SEQ ID NO:104)
5'- GCCACCCTAC-3' (SEQ ID NO:105)

NFAT:

5'- TATGAAACAGTTTTTCC –3' (SEQ ID NO:106)
5'- AGGAAACTC –3' (SEQ ID NO:107)
5'- ARGARATTCC –3' (SEQ ID NO:108)
5'- CCAGTTGAGCCAGAGA –3' (SEQ ID NO:109)

GAS:

5'- CTTTCAGTTTCATATTACTCTAAATCCATT –3' (SEQ ID NO:110)

p53 Binding Site :

p53 Consensus site:
5'- RRRCWWGYYY –3' (SEQ ID NO:111)

Examples of p53 binding sites:
5'- AGGCATGCCT –3' (SEQ ID NO:112)
5'- GGGCTTGCCC –3' (SEQ ID NO:113)
5'- GGGCTTGCTT –3' (SEQ ID NO:114)
5'- GCCTGGACTTGCC –3' (SEQ ID NO:115)
5'- GGACATGCCCGGGCATGTCC –3' (SEQ ID NO:116)
5'- GTAGCATTAGCCCAGACATGTCC –3' (SEQ ID NO:117)

TARE (TNF-α response element):
e.g. from the COL1A1 promoter

5'GAGGTATGCAGACAAGAGTCAGAGTTTCCCCTTGAA 3' (SEQ ID NO:118)

SRF

5'- CCWWWWWWGG –3' (SEQ ID NO:119)
5'- CCAAATAAGGC –3' (SEQ ID NO:120)

The TLR responsive promoter element can be derived from the promoter of a naturally occurring (i.e., an endogenous) gene that is activated or inhibited by TLR signaling (such as the IL-6 gene, the IL-8 gene, the IL-10 gene, the IL-12 p40 gene, the IP-9 gene, the IP-10 gene, the type 1 IFN gene, the IFN-α4 gene, the IFN-β gene, the TNF-α gene, the TNF-β gene, the RANTES gene, the ITAC gene, the IGFBP4 gene, the CD54 gene, the CD69 gene, the CD71 gene, the CD80 gene, the CD86 gene, the HLA-DR gene, the HLA class I gene, and the like). The afore-mentioned genes are genes that are known to be activated in response to TLR interaction with its ligand.

Suitable promoter regions are described in the Examples. Briefly, the upstream (5') –620 to +50 promoter region of IFN-α4 or the upstream (5') –140 to +9 promoter region of IFN-α1 can be used. In one embodiment, the IFN-α4 sequence is cloned into the *Sma*I site of the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') promoter region of IFN-α4.

The promoter can also be the upstream (5') –280 to +20 promoter region of IFN-β.

The promoter can also be the upstream (5') –397 to +5 promoter region of RANTES. In one embodiment, the RANTES promoter sequence is cloned into the NheI site (filled in with Klenow) of the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') –397 to +5 promoter region of RANTES.

The promoter can also be the upstream truncated (-250 to +30) and full length (-860 to +30) promoter regions derived from human IL-12 p40 genomic DNA. In one embodiment, the truncated IL-12 p40 promoter was cloned as a KpnI-XhoI insert into pβgal-Basic (Promega) resulting in an expression vector that includes a β gal gene under the control of the upstream (5') –250 to +30 promoter region of human IL-12 p40. In another embodiment, the full length IL-12 p40 promoter was cloned as a KpnI-XhoI insert into pβgal-Basic (Promega) resulting in an expression vector that includes a β gal gene under the control of the upstream (5') –751 to +30 promoter region of human IL-12 p40. In another embodiment, the truncated –250 to +30 promoter region of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') –250 to +30 promoter region of human IL-12 p40. In yet another embodiment, the full length IL-12 p40 promoter of human IL-12 p40 was cloned into the

pGL3-Basic Vector (Promega) resulting in an expression vector that includes a luciferase gene under the control of the upstream (5') –751 to +30 promoter region of human IL-12 p40.

The promoter can also be the upstream (5') -288 to +7 promoter region derived from human IL-6 genomic DNA. The promoter can also be derived from the full-length promoter region of the IL-6 gene from –1174 to + 7 (Accession No M22111, SEQ ID NO:129).

The promoter can also be the upstream (5') -734 to +44 or the upstream (5') -162 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J Immunol* 143:1366-71.

The promoter can also be derived from the -615 to +30 promoter region of human TNF-α.

The promoter can also be derived from a promoter region of human TNF-β.

The promoter can also be derived from the –875 to +97 promoter region of human IP-10.

The promoter can also be derived from the –219 to +114 promoter region of human CXCL11 (IP9). The promoter can also be derived from the full length (-934 to +114) promoter region of human CXCL11 (IP9).

The promoter can also be derived from the -289 to +217 promoter region of human IGFBP4 (Insulin growth factor binding protein 4). The promoter can also be derived from the full length (-836 to +217) promoter region of human IGFBP4.

The promoter response element generally will be present in multiple copies, e.g., as tandem repeats. For example, in one reporter construct, coding sequence for luciferase is under control of an upstream 6X tandem repeat of NF-κB response element. In another example, an ISRE-luciferase reporter construct useful in the invention is available from Stratagene (catalog no. 219092) and includes a 5x ISRE tandem repeat joined to a TATA box upstream of a luciferase reporter gene.

The reporter construct coding sequence is preferably any nucleotide sequence that codes for a protein capable of detection or quantification. The protein can be an enzyme (e.g., luciferase, alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase (CAT), secreted alkaline phosphatase, etc.), a bioluminescence marker (e.g., green fluorescent protein (GFP, U.S. Pat. No. 5,491,084), etc.), blue fluorescent protein (BFP, e.g., U.S. Pat. No. 6,486,382), etc.), a surface-expressed molecule (e.g., CD25, CD80, CD86), a secreted molecule (e.g., IL-1, IL-6, IL-8, IL-12 p40, TNF-α), a hapten or antigen, and other detectable protein products known to those of skill in the art. For assays relying on enzyme activity

readout, substrate can be supplied as part of the assay, and detection can involve measurement of chemiluminescence, fluorescence, color development, incorporation of radioactive label, drug resistance, or other marker of enzyme activity. For assays relying on surface expression of a molecule, detection can be accomplished using flow cytometry (FACS) analysis or functional assays. Secreted molecules can be assayed using enzyme-linked immunosorbent assay (ELISA) or bioassays. Many of these and other suitable readout systems are well known in the art and are commercially available. Preferably, the coding sequence encodes a protein having a level or an activity that is quantifiable, preferably with a wide linear range.

The expression construct coding sequence is preferably a TLR coding sequence derived from the sequences listed herein. Preferably, the expression construct promoter is a constitutive promoter, although in some embodiments it may be inducible. Those of ordinary skill in the art are familiar with such promoters.

As used herein, a coding sequence and the regulatory sequences (such as promoters) are said to be operably linked when they are covalently linked in such a way as to place the expression or transcription and/or translation of the coding sequence under the influence or control of the regulatory sequence. Two DNA sequences are said to be operably linked if induction of a promoter in the 5' regulatory sequence results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a regulatory sequence would be operably linked to a coding sequence if the gene expression sequence were capable of effecting transcription of that coding sequence such that the resulting transcript is translated into the desired protein or polypeptide.

Methods for nucleic acid introduction into cells are known in the art.

The nucleic acid may be delivered to the cells alone or in association with a vector. In its broadest sense, a vector is any vehicle capable of facilitating the transfer of the nucleic acid to the cells so that the reporter can be expressed. The vector generally transports the nucleic acid to the cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In general, the vectors useful in the invention include, but are not limited to, plasmids, phagemids, viruses, other vehicles derived from viral or bacterial sources that have been manipulated by the insertion or incorporation of the antigen nucleic acid sequences. Viral vectors are a preferred type of vector and include, but are not limited

to, nucleic acid sequences from the following viruses: retrovirus, such as Moloney murine leukemia virus, Harvey murine sarcoma virus, murine mammary tumor virus, and Rous sarcoma virus; adenovirus, adeno-associated virus; SV40-type viruses; polyoma viruses; Epstein-Barr viruses; papilloma viruses; herpes virus; vaccinia virus; polio virus; and RNA virus such as a retrovirus. One can readily employ other vectors not named but known in the art.

Preferred viral vectors are based on non-cytopathic eukaryotic viruses in which non-essential genes have been replaced with the gene of interest. Non-cytopathic viruses include retroviruses, the life cycle of which involves reverse transcription of genomic viral RNA into DNA with subsequent proviral integration into host cellular DNA. Retroviruses have been approved for human gene therapy trials. Most useful are those retroviruses that are replication-deficient (i.e., capable of directing synthesis of the desired proteins, but incapable of manufacturing an infectious particle). Such genetically altered retroviral expression vectors have general utility for the high-efficiency transduction of genes *in vivo*. Standard protocols for producing replication-deficient retroviruses (including the steps of incorporation of exogenous genetic material into a plasmid, transfection of a packaging cell lined with plasmid, production of recombinant retroviruses by the packaging cell line, collection of viral particles from tissue culture media, and infection of the target cells with viral particles) are provided in Kriegler, M., Gene Transfer and Expression, A Laboratory Manual W.H. Freeman C.O., New York (1990) and Murray, E.J. Methods in Molecular Biology, vol. 7, Humana Press, Inc., Cliffton, New Jersey (1991).

A preferred virus for certain applications is the adeno-associated virus, a double-stranded DNA virus. The adeno-associated virus can be engineered to be replication -deficient and is capable of infecting a wide range of cell types and species. It further has advantages such as, heat and lipid solvent stability; high transduction frequencies in cells of diverse lineages, including hemopoietic cells; and lack of superinfection inhibition thus allowing multiple series of transductions. Reportedly, wild-type adeno-associated virus manifest some preference for integration sites into human cellular DNA, thereby minimizing the possibility of insertional mutagenesis and variability of inserted gene expression characteristic of retroviral infection. In addition, wild-type adeno-associated virus infections have been followed in tissue culture for greater than 100 passages in the absence of selective pressure, implying that the adeno-associated virus genomic integration is a relatively stable event. The adeno-associated virus can also function in an extrachromosomal fashion.

Recombinant adeno-associated viruses that lack the replicase protein apparently lack this integration sequence specificity.

Other vectors include plasmid vectors. Plasmid vectors have been extensively described in the art and are well-known to those of skill in the art. See e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. In the last few years, plasmid vectors have been found to be particularly advantageous for delivering genes to cells *in vivo* because of their inability to replicate within and integrate into a host genome. These plasmids, however, having a promoter compatible with the host cell, can express a peptide from a gene operatively encoded within the plasmid. Some commonly used plasmids include pBR322, pUC18, pUC19, pRc/CMV, SV40, and pBlueScript. Other plasmids are well-known to those of ordinary skill in the art. Additionally, plasmids may be custom designed using restriction enzymes and ligation reactions to remove and add specific fragments of DNA.

In general, the vectors useful in the invention are divided into two classes: biological vectors and chemical/physical vectors. Biological vectors and chemical/physical vectors are useful in the delivery and/or uptake of reporter constructs of the invention.

Most biological vectors are used for delivery of nucleic acids and thus would be most appropriate in the delivery of nucleic acids.

As used herein, a "chemical/physical vector" refers to a natural or synthetic molecule, other than those derived from bacteriological or viral sources, capable of delivering the reference and test compound.

A preferred chemical/physical vector of the invention is a colloidal dispersion system. Colloidal dispersion systems include lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system of the invention is a liposome. Liposomes are artificial membrane vessels which are useful as a delivery vector *in vivo* or *in vitro*. It has been shown that large unilamellar vessels (LUV), which range in size from 0.2 - 4.0 μm can encapsulate large macromolecules. RNA, DNA and intact virions can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., *Trends Biochem. Sci.*, (1981) 6:77).

Liposomes may be targeted to a particular tissue by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein. Ligands which may be useful for targeting a liposome to an immune cell include, but are not limited to, intact or fragments of molecules which interact with immune cell specific receptors and molecules,

such as antibodies, which interact with the cell surface markers of immune cells. Such ligands may easily be identified by binding assays well known to those of skill in the art. In still other embodiments, the liposome may be targeted to the cancer by coupling it to a one of the immunotherapeutic antibodies discussed earlier. Additionally, the vector may be coupled to a nuclear targeting peptide, which will direct the vector to the nucleus of the host cell.

Lipid formulations for transfection are commercially available from QIAGEN, for example, as EFFECTENE™ (a non-liposomal lipid with a special DNA condensing enhancer) and SUPERFECT™ (a novel acting dendrimeric technology).

Liposomes are commercially available from Gibco BRL, for example, as LIPOFECTIN™ and LIPOFECTACE™, which are formed of cationic lipids such as N-[1-(2, 3 dioleyloxy)-propyl]-N, N, N-trimethylammonium chloride (DOTMA) and dimethyl dioctadecylammonium bromide (DDAB). Methods for making liposomes are well known in the art and have been described in many publications. Liposomes also have been reviewed by Gregoriadis, G. in *Trends in Biotechnology*, (1985) 3:235-241. In some preferred embodiments, the method of choice for delivering DNA (for transfection) to the cells is electroporation, particularly where a stably transfected cell line is sought.

The present invention is further illustrated by the following Examples, which in no way should be construed as further limiting.

Examples

Example 1. Biological Activity of Production Lot of CpG ODN (SEQ ID NO:1) Assayed Using Cells Stably Transfected with hTLR9 Expression Vector

CpG ODN (SEQ ID NO:1) is currently in preclinical and clinical trials for a number of clinical applications. SEQ ID NO:1 has been discovered to induce signaling through TLR9. In order to assess different lots of clinical material, the methods of the invention are employed, using a highly characterized lot of SEQ ID NO:1 as a reference.

In a TLR9 assay, the CpG-non-responsive human embryonal kidney cell line HEK293 (e.g., ATCC CRL-1573) was stably transfected with a hTLR9 expression construct and found to express full-length human TLR9 constitutively. The cells also contained a genomic copy of a reporter construct with a 6x NF-κB binding site and a luciferase gene reporter cassette. Incubation of the cells with CpG ODN (SEQ ID NO:1) activates NF-κB driven expression of luciferase, while incubation with medium alone (negative control) does not. The cells are

then lysed and activity of the luciferase protein determined by its catalytic activity of luciferin oxidation which is measured in a luminometer. Results are expressed as fold induction above medium control.

Assay set-up includes a reference standard material which is highly pure and well characterized. The reference material is used to create a standard curve within a defined range where the dose-response curve is linear (e.g., in the range of the EC50 value for SEQ ID NO:1, 70-100 nM). The test material is dissolved for testing and assayed at a defined concentration. Activity of the test material is calculated using the standard curve of the reference material. Quality of the tested material is deemed acceptable if activity of the test material compared to activity of the reference material falls within predetermined limits.

Example 2. Biological Activity of Production Lot of CpG ODN (SEQ ID NO:1) Assayed Using RPMI 8226 Cells

The assay of Example 1 is performed using RPMI 8226 cells (ATCC CCL-155) in place of the stably transfected HEK cells of Example 1. RPMI 8226 cells naturally express human TLR9. The cells are stably transfected with a 6x NF-κB-luciferase reporter construct. It is to be understood that the assay could also be carried out by measuring a native readout such as IL-10 secretion.

Example 3. Expression Vectors for Human TLR3 (hTLR3) and Murine TLR3 (mTLR3)

To create an expression vector for human TLR3, human TLR3 cDNA was amplified by the polymerase chain method (PCR) from a cDNA made from human 293 cells using the primers 5'-GAAACTCGAGCCACCATGAGACAGACTTTGCCTTGTATCTAC-3' (sense, SEQ ID NO:152) and 5'-GAAAGAATTCTTAATGTACAGAGTTTTTGGATCCAAG-3' (antisense, SEQ ID NO:153). The primers introduce *Xho*I and *Eco*RI restriction endonuclease sites at their 5' ends for use in subsequent cloning into the expression vector. The resulting amplification product fragment was cloned into pGEM-T Easy vector (Promega), isolated, cut with *Xho*I and *Eco*RI restriction endonucleases, ligated into an *Xho*I/*Eco*RI-digested pcDNA3.1 expression vector (Invitrogen). The insert was fully sequenced and translated into protein. The cDNA sequence corresponds to the published cDNA sequence for hTLR3, available as GenBank accession no. NM_003265 (SEQ ID NO:7). The open reading frame codes for a protein 904 amino acids long, having the sequence corresponding to GenBank accession no. NP_003256 (SEQ ID NO:8).

Corresponding nucleotide and amino acid sequences for murine TLR3 (mTLR3) are known. The nucleotide sequence of mTLR3 cDNA has been reported as GenBank accession no. AF355152 (SEQ ID NO:9), and the amino acid sequence of mTLR3 has been reported as GenBank accession no. AAK26117 (SEQ ID NO:10).

Example 4. Reconstitution of TLR3 Signaling in 293 Fibroblasts

Human TLR3 cDNA and murine TLR3 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the *EcoRI* site. The resulting expression vectors mentioned above were transfected into CpG-DNA non-responsive human 293 fibroblast cells (ATCC, CRL-1573) using the calcium phosphate method. Utilizing a "gain of function" assay it was possible to reconstitute human TLR3 (hTLR3) and murine TLR3 (mTLR3) signaling in 293 fibroblast cells.

Since NF-κB activation is central to the IL-1/TLR signal transduction pathway (Medzhitov R et al. (1998) *Mol Cell* 2:253-8; Muzio M et al. (1998) *J Exp Med* 187:2097-101), in a first set of experiments human 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and an NF-κB-driven luciferase reporter construct.

Likewise, in a second set of experiments, 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and an IFN-α4-driven luciferase reporter construct (described in Example 8 below).

In a third group of experiments, 293 fibroblast cells were transfected with hTLR3 alone or co-transfected with hTLR3 and a RANTES-driven luciferase reporter construct (described in Example 14 below).

Example 5. Reconstitution of TLR7 Signaling

Methods for cloning murine and human TLR7 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are incorporated herein by reference. Human TLR7 cDNA and murine TLR7 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR7 (hTLR7) and murine TLR7 (mTLR7) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors

mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

Example 6. Reconstitution of TLR8 Signaling

Methods for cloning murine and human TLR8 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are incorporated by reference. Human TLR8 cDNA and murine TLR8 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR8 (hTLR8) and murine TLR8 (mTLR8) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

Example 7. Reconstitution of TLR9 Signaling in 293 Fibroblasts

Methods for cloning murine and human TLR9 have been described in pending U.S. Pat. Application No. 09/954,987 and corresponding published PCT application PCT/US01/29229 (WO 02/22809), both filed September 17, 2001, the contents of which are incorporated by reference. Human TLR9 cDNA and murine TLR9 cDNA in pT-Adv vector (from Clontech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR9 (hTLR9) and murine TLR9 (mTLR9) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

To generate stable clones expressing human TLR9, murine TLR9, or either TLR9 with the NF-κB-luc reporter plasmid, 293 cells were transfected in 10 cm plates ($2x10^6$ cells/plate) with 16 μg of DNA and selected with 0.7 mg/ml G418 (PAA Laboratories GmbH, Cölbe, Germany). Clones were tested for TLR9 expression by RT-PCR, for example as shown in Fig. 21. The clones were also screened for IL-8 production or NF-κB-luciferase activity after stimulation with ODN. Four different types of clones were generated.

293-hTLR9-luc:	expressing human TLR9 and 6x NF-κB–luciferase reporter
293-mTLR9-luc:	expressing murine TLR9 and 6x NF-κB–luciferase reporter
293-hTLR9:	expressing human TLR9
293-mTLR9:	expressing murine TLR9

Human 293 fibroblast cells were transiently transfected with hTLR9 and a 6x NF-κB-luciferase reporter plasmid (NF-κB-luc, kindly provided by Patrick Baeuerle, Munich, Germany) (Fig. 18A) or with hTLR9 alone (Fig. 18B). After stimulus with CpG-ODN (2μM, TCGTCGTTTTGTCGTTTTGTCGTT, SEQ ID NO:1), GpC-ODN (2μM, TGCTGCTTTTGTGCTTTTGTGCTT, SEQ ID NO:154), LPS (100 ng/ml) or media, NF-κB activation by luciferase readout (8h, Fig. 18A) or IL-8 production by ELISA (48h, Fig. 18B) was monitored. Results are representative of three independent experiments. Fig. 18 shows that cells expressing hTLR9 responded to CpG-DNA but not to LPS.

Human 293 fibroblast cells were transiently transfected with mTLR9 and the NF-κB-luc construct. Similar data was obtained for IL-8 production (not shown). Thus expression of TLR9 (human or mouse) in 293 cells results in a gain of function for CpG DNA stimulation similar to hTLR4 reconstitution of LPS responses.

Figs. 19 and 20 demonstrate the responsiveness of a stable 293-mTLR9-luc and 293-hTLR9-luc clones after stimulation with CpG-ODN (2μM, SEQ ID NO:1), GpC-ODN (2μM, SEQ ID NO:154), Me-CpG-ODN (2μM; TZGTZGTTTTGTZGTTTTGTZGTT, Z = 5-methylcytidine, SEQ ID NO:147), LPS (100 ng/ml) or media, as measured by monitoring NF-κB activation. Similar results were obtained utilizing IL-8 production with the stable clones. These results demonstrate that CpG-DNA non-responsive cell lines can be stably genetically complemented with TLR9 to become responsive to CpG DNA in a motif-specific manner.

Example 8. Method of Making IFN-α4 Reporter Vector

A number of reporter vectors may be used in the practice of the invention. Some of the reporter vectors are commercially available, e.g., the luciferase reporter vectors pNF-κB-Luc (Stratagene) and pAP1-Luc (Stratagene). These two reporter vectors place the luciferase gene under control of an upstream (5') promoter region derived from genomic DNA for NF-κB or AP1, respectively. Other reporter vectors can be constructed following standard

methods using the desired promoter and a vector containing a suitable reporter, such as luciferase, β-galactosidase (β-gal), chloramphenicol acetyltransferase (CAT), and other reporters known by those skilled in the art. Following are some examples of reporter vectors constructed for use in the present invention.

IFN-α4 is an immediate-early type 1 IFN. Sequence-specific PCR products for the –620 to +50 promoter region of IFN-α4 were derived from genomic DNA of human 293 cells and cloned into the *Sma*I site of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') –620 to +50 promoter region of IFN-α4. The sequence of the –620 to +50 promoter region of IFN-α4 is provided as SEQ ID NO:121.

Example 9. Method of Making IFN-α1 Reporter Vector

IFN-α1 is a late type 1 IFN. Sequence-specific PCR products for the –140 to +9 promoter region of IFN-α1 were derived from genomic DNA of human 293 cells and cloned into *Sma*I site of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') –140 to +9 promoter region of IFN-α1. A sequence of the –140 to +9 promoter region of IFN-α1 is provided as SEQ ID NO:122.

Example 10. Method of Making IFN-β Reporter Vector

IFN-β is an immediate-early type 1 IFN. The –280 to +20 promoter region of IFN-β was derived from the pUCβ26 vector (Algarté M et al. (1999) *J Virol* 73:2694-702) by restriction at *EcoR*I and *Taq*I sites. The 300 bp restriction fragment was filled in by Klenow enzyme and cloned into *Nhe*I-digested and filled in pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') –280 to +20 promoter region of IFN-β. A sequence of the –280 to +20 promoter region of IFN-β is provided as SEQ ID NO:123.

Example 11. Method of Making Human IL-6 Reporter Vectors

Reporter constructs are made using the -285 to +7 promoter region derived from human IL-6 genomic DNA. (Takeshita et al. Eur. J. Immunol. 2000. 30: 108–116.) In one reporter construct the IL-6 promoter region is cloned as a *Kpn*I-*Xho*I insert into pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of

an upstream (5') -288 to +7 promoter region derived from human IL-6 genomic DNA. A sequence of the –288 to +7 promoter region of human IL-6 is provided as SEQ ID NO:128.

The promoter can also be derived from the full-length promoter region of the IL-6 gene from –1174 to + 7 (GenBank Accession No M22111) as shown below as SEQ ID NO:129.

Example 12. Method of Making Human IL-8 Reporter Vectors

Reporter constructs have been made using a -546 to +44 and a truncated -133 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J Immunol* 143:1366-71. In each reporter construct the IL-8 promoter region was cloned as a *Kpn*I-*Xho*I insert into pGL3-Basic Vector (Promega). One of the resulting expression vectors includes a luciferase gene under control of an upstream (5') -546 to +44 promoter region derived from human IL-8 genomic DNA. Another of the resulting expression vectors includes a luciferase gene under control of an upstream (5') -133 to +44 promoter region derived from human IL-8 genomic DNA.

The promoter can also be the upstream (5') -734 to +44 or the upstream (5') -162 to +44 promoter region derived from human IL-8 genomic DNA. Mukaida N et al. (1989) *J Immunol* 143:1366-71. A sequence of the -734 to +44 promoter region derived from human IL-8 is provided below as SEQ ID NO: 130.

Example 13. Method of Making Human IL-12 p40 Reporter Vectors

Reporter constructs have been made using truncated (-250 to +30, SEQ ID NO:127) and full length (-751 to +30, SEQID NO:126) promoter regions derived from human IL-12 p40 genomic DNA. (Takeshita et al. Eur. J. Immunol. 2000. 30: 108–116.) In one reporter construct the truncated IL-12 p40 promoter was cloned as a *Kpn*I-*Xho*I insert into pβgal-Basic (Promega). The resulting expression vector includes a β gal gene under control of an upstream (5') –250 to +30 promoter region of human IL-12 p40. In a second reporter construct the full length IL-12 p40 promoter was cloned as a *Kpn*I-*Xho*I insert into pβgal-Basic (Promega). The resulting expression vector includes a β gal gene under control of an upstream (5') –751 to +30 promoter region of human IL-12 p40. In a third reporter construct the truncated –250 to +30 promoter region of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') –250 to +30 promoter region of human IL-12 p40. In a

fourth reporter construct the full length IL-12 p40 promoter of human IL-12 p40 was cloned into the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') –751 to +30 promoter region of human IL-12 p40. A sequence of the –751 to +30 promoter region of human IL-12 p40 is provided as SEQ ID NO: 126.

Example 14. Method of Making RANTES Reporter Vector

Transcription of the chemokine RANTES is believed to be regulated at least in part by IRF3 and by NF-κB. Lin R et al. (1999) *J Mol Cell Biol* 19(2):959-66; Genin P et al. (2000) *J Immunol* 164:5352-61. A 483 bp sequence-specific PCR product including the –397 to +5 promoter region of RANTES was derived from genomic DNA of human 293 cells, restricted with *Pst*I and cloned into pCAT-Basic Vector (Promega) using *Hind*III (filled in with Klenow) and *Pst*I sites (filled in). The –397 to +5 promoter region of RANTES was then isolated from the resulting RANTES/chloramphenicol acetyltransferase (CAT) reporter plasmid by restriction with *Bgl*II and *Sal*I, filled in with Klenow enzyme, and cloned into the *Nhe*I site (filled in with Klenow) of the pGL3-Basic Vector (Promega). The resulting expression vector includes a luciferase gene under control of an upstream (5') –397 to +5 promoter region of RANTES. Comparison of the insert sequence –397 to +5 of Genin P et al. (2000) *J Immunol* 164:5352-61 and GenBank accession no. AB023652 (SEQ ID NO:125) revealed two point deletions (at positions 105 and 273 of SEQ ID NO:125) which do not create new restriction sites. A sequence of the –397 to +5 promoter region of RANTES is provided as SEQ ID NO:125.

Example 15. RT-PCR Analysis of Cell Lines for TLR Expression

TLR expression was determined using total RNA of cells prepared by standard methods (QIAGEN). RNA was transcribed to cDNA using AMV Reverse Transcriptase (Roche). Quantitative PCR was performed with TLR-gene specific primer sets using a LightCycler Instrument (Roche). Controls for genomic DNA impurities were performed by a similar PCR method using RNA (but without reverse transciptase).

A variety of cell lines was screened for their expression of TLR3, 7, 8 and 9. These cell lines are A549 (human lung carcinoma), BeWo (human choriocarcinoma), HeLa (human cervix carcinoma), Hep-2 (human cervix carcinoma), KG-1 (human acute myeloid leukemia), MUTZ-3 (human acute myelomonocytic leukemia), Nalm-6 (human B cell precursor

leukemia), NK-92 (human Natural killer cell line), NK-92 MI (human Natural killer cell line, IL-2 independent), Raji (human Burkitt's lymphoma, B lymphocyte), RAMOS (Burkitt's lymphoma, B lymphocyte), RPMI 8226 (human multiple myeloma, B lymphocyte), THP-1 (human acute monocytic leukemia), U937 (human lymphoma) and Jurkat (human T cell leukemia).

All B cell lines express, as determined by Real Time-PCR (RT-PCR), endogenous TLR9. In addition, all lines except NALM co-express TLR7. Nevertheless, none of the other cell lines appeared to express TLR7, whereas low TLR9 expression on the mRNA level was observed for KG-1 and THP-1. TLR3 appeared to be expressed in most of these cell lines, with the highest mRNA levels for example in the NK cell lines (e.g., NK-92).

Raji cells contain high levels of TLR9 mRNA and low levels of TLR3 and TLR7 mRNA suggesting high expression of TLR9 protein and lower levels of TLR3 and TLR7 protein.

These results indicate that the cell lines expressing TLR9 can be used to screen potential new TLR9 ligands (CpG ODN, etc.), cell lines expressing TLR7 to screen potential new TLR7 ligands (ORN (oligoribonucleotides), small molecules, etc.), and cell lines expressing both receptors may be used to screen for "hybrid" TLR7 and 9 agonists. In addition, cell lines lacking TLR8 expression (i.e., all cell lines tested) can be used to confirm the specificity of a TLR7 versus a TLR8 ligand (i.e., the latter should not be able to stimulate TLR7-expressing cells). In contrast, cell lines expressing TLR3 (e.g., Raji cells) may be used to screen for potential new TLR3 ligands (dsRNA, etc.).

Example 16. Screening of Various Cell Lines for Responses to TLR Ligands

Except where otherwise indicated, the following general methods were used. Cells were plated at 5 x 10^5/ml in 48 well plates in RPMI medium with 10% FBS. Stimulation was performed by addition of the oligonucleotides or other compounds diluted to the test concentrations in TE. Cells were incubated for 24 or 48h and the supernatants were taken to analyse for the presence of cytokines or chemokines.

The TLR ligands used are as follows:

TLR3: Poly I:C

TLR7, TLR8: R-848

TLR9:

T*C*C*A*G*G*A*C*T*T*C*T*C*T*C*A*G*G*T*T (SEQ ID NO: 2);

T*C*G*T*C*G*T*T*T*T*G*T*C*G*T*T*T*T*G*T*C*G*T*T (SEQ ID NO: 1);
T*G*C*T*G*C*T*T*T*T*G*T*G*C*T*T*T*T*G*T*G*C*T*T (SEQ ID NO: 154);
T*C*G*T*C*G*T*T*T*T*C*G*G*C*G*C*G*C*G*C*C*G (SEQ ID NO: 158);
G*G*G_G_A_C_G_A_C_G_T_C_G_T_G_G*G*G*G*G*G (SEQ ID NO: 159);
T*G*C*T*G*C*T*T*T*T*C*G*G*C*G*G*C*C*G*C*C*G (SEQ ID NO: 160);
G*G*G_G_A_G_C_A_G_C_T_G_C_T_G_G*G*G*G*G*G (SEQ ID NO: 161).
* phosphorothioate linkage; _ phosphodiester linkage.

Increased expression of cell surface markers was determined using cells stimulated as described above and then stained with different monoclonal antibody combinations specific for the cell surface markers. Analysis of the cells was performed by flow cytometry.

Changes in reporter gene activity were determined using cells transfected with a NF-κB reporter construct (Stratagene) and a β-galactosidase reporter control plasmid (Invitrogen) using electroporation. For NF-κB analysis, a 5x NF-κB-Luciferase Vector (Stratagene) was used. The amount of DNA transfected as well as cell concentration was varied. Stimulation was performed 24h after transfection. Cells were stimulated with the indicated amounts of ODN, R-848, LPS, TNF-α, or IL-1 β for the indicated incubation times. Cell extracts were prepared by lysing the cells in 100 μl reporter lysis buffer (Promega) using the freeze-thaw method. All data were normalized for β-galactosidase expression. Stimulation indices were calculated in reference to luciferase activity of medium without addition of ODN.

Stimulation of the Raji cell line with a TLR9 ligand (CpG ODN), a TLR3 ligand (poly I:C) or a TLR7 ligand (R-848) results in the ligand-specific secretion of cytokines. Figs. 14 and 15 show IL-6 production of Raji cells upon stimulation with ODN, poly I:C or R-848. Fig. 16 shows IFN-α2 production of Raji cells upon stimulation with ODN, poly I:C or R-848. In all assays, cells were incubated with Na-Butyrate for 48h before stimulation with TLR ligands. CpG stimulation of the RAMOS cell lines can result in the CpG-specific up-regulation of cell surface markers such as CD80, as shown in Fig. 17.

Example 17. Inhibition of a Positive Reference Compound Response with an Inhibitory Test Compound

Inhibition of CpG mediated chemokine production was determined using RPMI 8226 cells incubated with increasing amounts of SEQ ID NO:1 in the presence of an

immunoinhibitory ODN (SEQ ID NO: 151). IP-10 production was measured 24h later by ELISA (Fig. 9).

Equivalents

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

We claim:

Claims

1. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting an RPMI 8226 cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the TLR signaling activity is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-8 production, IL-8 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF-α expression, TNF-α production and TNF-α secretion.

2. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of an immunostimulatory compound, and

wherein the cell is a Raji cell, a RAMOS cell, a Nalm cell, a THP-1 cell, or a KG-1 cell.

3. The method of claim 1 or 2, wherein the test level is positive relative to a reference level determined by contacting the cell with a reference compound and measuring a reference TLR signaling activity.

4. The method of claim 3, wherein the reference compound is a positive reference compound

5. The method of claim 4, wherein the positive reference compound is selected from the group consisting of an immunostimulatory nucleic acid and an imidazoquinoline compound.

6. The method of claim 3, wherein the reference compound is a negative reference compound.

7. The method of claim 6, wherein the negative reference compound is medium alone.

8. The method of claim 5, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

9. The method of claim 5, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

10. The method of claim 1 or 2, wherein the test compound is a nucleic acid.

11. The method of claim 10, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif.

12. The method of claim 10, wherein the nucleic acid comprises a phosphorothioate backbone linkage.

13. The method of claim 10, wherein the nucleic acid is a DNA, an RNA or a DNA-RNA hybrid.

14. The method of claim 1 or 2, wherein the test compound is a non-nucleic acid small molecule.

15. The method of claim 1 or 2, wherein the test compound comprises an amino acid, a carbohydrate, a lipid, or a hormone.

16. The method of claim 15, wherein the carbohydrate is a polysaccharide.

17. The method of claim 1 or 2, wherein the test compound is derived from a molecular library.

18. The method of claim 1, wherein the cell is transfected with a nucleic acid.

19. The method of claim 18, wherein the nucleic acid encodes a TLR or a reporter construct.

20 . The method of claim 2, wherein the cell is transfected with a nucleic acid.

21. The method of claim 20, wherein the nucleic acid encodes a TLR or a reporter construct.

22. The method of claim 19 or 21, wherein the TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.

23. The method of claim 22, wherein the TLR is a human TLR.

24. The method of claim 19 or 21, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a β-galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.

25. The method of claim 19 or 21, wherein the reporter construct comprises a TLR responsive promoter.

26. The method of claim 25, wherein the TLR responsive promoter comprises a transcription factor binding site selected from the group consisting of a NF-κB binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an

IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

27. The method of claim 25, wherein the TLR responsive promoter is a promoter region selected from the group consisting of an IL-1 promoter region, an IL-6 promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter region, an IFN-α1 promoter region, an IFN-α4 promoter region, an IFN-β promoter region, an IFN-γ promoter region, a TNF-α promoter region, a TNF-β promoter region, an IP-9 promoter region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69 promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region, a HLA-DR promoter region, and a HLA class I promoter region.

28. The method of claim 18 or 20, wherein the cell is stably transfected.

29. The method of claim 1 or 2, wherein the TLR signaling activity is measured by cytokine secretion or chemokine secretion.

30. The method of claim 1, wherein the TLR signaling activity is selected from the group consisting of IL-8 secretion, IL-10 secretion, IP-10 secretion and TNF-α secretion.

31. The method of claim 2, wherein the TLR signaling activity is selected from the group consisting of IL-6 expression, IL-6 production, IL-6 secretion, IL-8 expression, IL-8 production, IL-8 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IP-10 expression, IP-10 production, IP-10 secretion, IL-12 expression, IL-12 production, IL-12 secretion, TNF-α expression, TNF-α production and TNF-α secretion.

32. The method of claim 2, wherein the TLR signaling activity is measured by phosphorylation.

33. The method of claim 32, wherein phosphorylation is total cellular phosphorylation.

34. The method of claim 32, wherein phosphorylation is phosphorylation of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NFkB subunits, c-Jun and c-Fos.

35. The method of claim 1 or 2, wherein the TLR signaling activity is measured by gene expression.

36. The method of claim 1, wherein the TLR signaling activity is measured by gene expression selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-10 expression, IP-10 expression, and TNF-α expression.

37. The method of claim 35, wherein TLR signaling activity is measured by microarray techniques.

38. The method of claim 2, wherein the TLR signaling activity is measured by cell proliferation.

39. The method of claim 1 or 2, wherein TLR signaling activity is measured by cell surface marker expression.

40. The method of claim 1, wherein TLR signaling activity is measured by cell surface expression of CD71, CD86 or HLA-DR.

41. The method of claim 2, wherein TLR signaling activity is measured by CD71 cell surface expression, CD86 cell surface expression, HLA-DR cell surface expression, CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

42. The method of claim 2, wherein TLR signaling activity is measured by antibody secretion.

43. The method of claim 42, wherein the antibody secretion is IgM secretion.

44. A composition comprising
an RPMI 8226 cell stably transfected with a nucleic acid encoding a TLR polypeptide, or a fragment thereof.

45. The composition of claim 44, further comprising a reporter construct comprising a promoter and a reporter sequence wherein the promoter is a TLR responsive promoter.

46. The composition of claim 45, wherein the TLR responsive promoter comprises a nucleic acid sequence selected from the group consisting of an NF-κB binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

47. The composition of claim 45, wherein the reporter sequence is selected from the group consisting of a luciferase sequence, a *β*-galactosidase sequence, a green fluorescent protein sequence, a secreted alkaline phosphatase sequence and a chloramphenicol transferase sequence.

48. The composition of claim 44, wherein the TLR polypeptide or fragment thereof is a human TLR polypeptide or fragment thereof.

49. The composition of claim 44, wherein the TLR polypeptide or fragment thereof is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.

50. The composition of claim 44, wherein the TLR polypeptide or fragment thereof is a human TLR polypeptide.

51. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting an cell that ectopically expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the cell that ectopically expresses a TLR is selected from the group consisting of RPMI 8226, RAMOS, Raji, Nalm, THP-1, KG-1 and 293 HEK.

52. The method of claim 51, wherein the test level is positive relative to a reference level determined by contacting the cell with a reference compound and measuring a reference TLR signaling activity.

53. The method of claim 52, wherein the reference compound is a positive reference compound.

54. The method of claim 53, wherein the positive reference compound is selected from the group consisting of an immunostimulatory nucleic acid and an imidazoquinoline compound.

55. The method of claim 54, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

56. The method of claim 54, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

57. The method of claim 52, wherein the reference compound is negative reference compound.

58. The method of claim 57, wherein the negative reference compound is medium alone.

59. The method of claim 51, wherein the test compound is a nucleic acid.

60. The method of claim 59, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif.

61. The method of claim 59, wherein the nucleic acid comprises a phosphorothioate backbone linkage.

62. The method of claim 59, wherein the nucleic acid is a DNA, an RNA, or a DNA-RNA hybrid.

63. The method of claim 51, wherein the test compound is a non-nucleic acid small molecule.

64. The method of claim 51, wherein the test compound comprises an amino acid, a carbohydrate, a lipid, or a hormone.

65. The method of claim 64, wherein the carbohydrate is a polysaccharide.

66. The method of claim 51, wherein the test compound is derived from a molecular library.

67. The method of claim 51, wherein the TLR signaling activity is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-6 expression, IL-6 production, IL-6 secretion, IL-8 expression, IL-8 production, IL-8 secretion, IL-10 expression, IL-10 production, IL-10 secretion, IL-12 expression, IL-12 production, IL-12 secretion, IP-10 expression, IP-10 production, IP-10 secretion, TNF-α expression, TNF-α production and TNF-α secretion.

68. The method of claim 51, wherein the TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.

69. The method of claim 51, wherein the TLR is a human TLR.

70. The method of claim 51, wherein the cell is transfected with a reporter construct.

71. The method of claim 70, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a β-galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.

72. The method of claim 71, wherein the TLR signaling activity is measured by luciferase expression, β-galactosidase expression, chloramphenicol expression, acetyltransferase expression, green fluorescent protein expression, alkaline phosphatase expression and alkaline phosphatase secretion.

73. The method of claim 71, wherein the reporter construct comprises a TLR responsive promoter.

74. The method of claim 25 or 73, wherein the TLR responsive promoter is a TLR1 responsive promoter, a TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter and a TLR10 responsive promoter.

75. The method of claim 73, wherein the TLR responsive promoter comprises a transcription factor binding site selected from the group consisting of an NF-κB binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

76. The method of claim 73, wherein the TLR responsive promoter is a promoter region selected from the group consisting of an IL-1 promoter region, an IL-6 promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter region, an IFN-α1 promoter region, an IFN-α4 promoter region, an IFN-β promoter region, an IFN-γ promoter region, a TNF-α promoter region, a TNF-β promoter region, an IP-9 promoter

region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69 promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region, a HLA-DR promoter region, and a HLA class I promoter region.

77. The method of claim 51, wherein the cell is stably transfected with a TLR nucleic acid.

78. The method of claim 70, wherein the cell is stably transfected with the reporter construct.

79. The method of claim 51, wherein the TLR signaling activity is measured by cytokine secretion or chemokine secretion.

80. The method of claim 79, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-8 secretion, TNF-α secretion, IL-10 secretion and IP-10 secretion.

81. The method of claim 79, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-6 secretion and IL-12 secretion.

82. The method of claim 51, wherein the TLR signaling activity is measured by phosphorylation.

83. The method of claim 82, wherein phosphorylation is total cellular phosphorylation.

84. The method of claim 82, wherein phosphorylation is phosphorylation of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NF-κB subunits, c-Jun and c-Fos.

85. The method of claim 51, wherein the TLR signaling activity is measured by gene expression.

86. The method of claim 85, wherein the gene expression is selected from the group consisting of IL-8 expression, IL-10 expression, IP-10 expression, CD71 expression, CD86 expression and HLA-DR expression.

87. The method of claim 85, wherein the gene expression is selected from the group consisting of IL-6 expression, IL-12 expression and TNF-α expression.

88. The method of claim 51, wherein the TLR signaling activity is measured by microarray techniques.

89. The method of claim 51, wherein the TLR signaling activity is measured by cell proliferation.

90. The method of claim 51, wherein the TLR signaling activity is measured by cell surface marker expression.

91. The method of claim 90, wherein the cell surface marker expression is selected from the group consisting of CD71 cell surface expression, CD86 cell surface expression and HLA-DR cell surface expression.

92. The method of claim 90, wherein the cell surface marker expression is selected from the group consisting of CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

93. The method of claim 51, wherein the TLR signaling activity is measured by antibody secretion.

94. The method of claim 93, wherein the antibody secretion is IgM secretion.

95. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

wherein a test level that is less than a reference level is indicative of test compound that is a TLR antagonist, and

wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell, a Raji cell, a THP-1 cell, a Nalm cell and a KG-1 cell.

96. The method of claim 95, wherein the positive reference compound is selected from the group consisting of an immunostimulatory nucleic acid and an immunostimulatory imidazoquinoline compound.

97. The method of claim 96, wherein the immunostimulatory nucleic acid is selected from the group consisting of a CpG nucleic acid, a T-rich nucleic acid, a poly-T nucleic acid and a poly-G nucleic acid.

98. The method of claim 96, wherein the imidazoquinoline compound is selected from the group consisting of R-848 and R-847.

99. The method of claim 95, wherein the test compound is a nucleic acid.

100. The method of claim 99, wherein the nucleic acid does not comprise a motif selected from the group consisting of a CpG motif, a poly-T motif, a T-rich motif and a poly-G motif.

101. The method of claim 99, wherein the nucleic acid comprises a phosphorothioate backbone linkage.

102. The method of claim 99, wherein the nucleic acid is a DNA, an RNA or a DNA-RNA hybrid.

103. The method of claim 95, wherein the test compound is a non-nucleic acid small molecule.

104. The method of claim 95, wherein the test compound comprises an amino acid, a carbohydrate, a lipid, or a hormone.

105. The method of claim 104, wherein the carbohydrate is a polysaccharide.

106. The method of claim 95, wherein the test compound is derived from a molecular library.

107. The method of claim 95, wherein the experimental cell is transfected with a nucleic acid.

108. The method of claim 107, wherein the nucleic acid encodes a TLR or a reporter construct.

109. The method of claim 108, wherein the TLR is selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9 and TLR10.

110. The method of claim 108, wherein the TLR is a human TLR.

111. The method of claim 108, wherein the reporter construct is selected from the group consisting of a luciferase reporter construct, a β-galactosidase reporter construct, a chloramphenicol acetyltransferase reporter construct, a green fluorescent protein reporter construct, and a secreted alkaline phosphatase construct.

112. The method of claim 111, wherein the TLR signaling activity is selected from the group consisting of luciferase expression, β-galactosidase expression, chloramphenicol acetyltransferase expression, green fluorescent protein expression, alkaline phosphatase expression and alkaline phosphatase secretion.

113. The method of claim 108, wherein the reporter construct comprises a TLR responsive promoter.

114. The method of claim 113, wherein the TLR responsive promoter comprises a transcription factor binding site selected from the group consisting of an NF-κB binding site, an AP-1 binding site, a CRE, a SRE, an ISRE, a GAS, an ATF2 binding site, an IRF3 binding site, an IRF7 binding site, an NFAT binding site, a p53 binding site, an SRF binding site, and a TARE.

115. The method of claim 113, wherein the TLR responsive promoter is a promoter region selected from the group consisting of an IL-1 promoter region, an IL-6 promoter region, an IL-8 promoter region, an IL-10 promoter region, an IL-12 p40 promoter region, an IFN-α1 promoter region, an IFN-α4 promoter region, an IFN-β promoter region, an IFN-γ promoter region, a TNF-α promoter region, a TNF-β promoter region, an IP-9 promoter region, an IP-10 promoter region, a RANTES promoter region, an ITAC promoter region, a MCP-1 promoter region, an IGFBP4 promoter region, a CD54 promoter region, a CD69 promoter region, a CD71 promoter region, a CD80 promoter region, a CD86 promoter region, a HLA-DR promoter region, and a HLA class I promoter region.

116. The method of claim 113, wherein the TLR responsive promoter is selected from the group consisting of a TLR1 responsive promoter, TLR2 responsive promoter, a TLR3 responsive promoter, a TLR4 responsive promoter, a TLR5 responsive promoter, a TLR6 responsive promoter, a TLR7 responsive promoter, a TLR8 responsive promoter, a TLR9 responsive promoter and a TLR10 responsive promoter.

117. The method of claim 107, wherein the cell is stably transfected with the nucleic acid.

118. The method of claim 95, wherein the TLR signaling activity is measured by cytokine secretion or chemokine secretion.

119. The method of claim 118, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-6 secretion, IL-12 secretion and TNF-α secretion.

120. The method of claim 118, wherein the cytokine secretion or chemokine secretion is selected from the group consisting of IL-8 secretion, IL-10 secretion and IP-10 secretion.

121. The method of claim 95, wherein the TLR signaling activity is measured by phosphorylation.

122. The method of claim 121, wherein phosphorylation is total cellular phosphorylation.

123. The method of claim 122, wherein phosphorylation is phosphorylation of a factor selected from the group consisting of IRAK, ERK, MyD88, TRAF6, p38, NF-κB subunits, c-Jun and c-Fos.

124. The method of claim 95, wherein the TLR signaling activity is measured by gene expression.

125. The method of claim 124, wherein the gene expression is selected from the group consisting of CD71 expression, CD86 expression, HLA-DR expression, IL-8 expression, IL-10 expression and IP-10 expression.

126. The method of claim 124, wherein the gene expression is selected from the group consisting of IL-6 expression, IL-12 expression and TNF-α expression.

127. The method of claim 95, wherein the TLR signaling activity is measured by microarray techniques.

128. The method of claim 95, wherein the TLR signaling activity is measured by cell proliferation.

129. The method of claim 95, wherein the TLR signaling activity is measured by cell surface marker expression.

130. The method of claim 129, wherein the cell surface marker expression is selected from the group consisting of CD71 cell surface expression, CD86 cell surface expression and HLA-DR MHC class II cell surface expression.

131. The method of claim 129, wherein the cell surface marker expression is selected from the group consisting of CD80 cell surface expression, HLA class I cell surface expression, CD54 cell surface expression and CD69 cell surface expression.

132. The method of claim 95, wherein the TLR signaling activity is measured by antibody secretion.

133. The method of claim 132, wherein the antibody secretion is IgM secretion.

134. The method of claim 95, wherein the cell is contacted to the positive reference compound and the test compound simultaneously.

135. The method of claim 95, wherein the cell is contacted to the positive reference compound prior to contact with the test compound.

136. The method of claim 95, wherein the cell is contacted to the test compound prior to contact with the positive reference compound.

137. A method for quality assessment of a test composition containing a known Toll like receptor (TLR) ligand, comprising:

measuring a reference activity of a reference composition comprising a known TLR ligand, wherein the known TLR ligand is a nucleic acid molecule;

measuring a test activity of a test composition comprising the known TLR ligand; and

comparing the test activity to the reference activity.

138. The method of claim 137, further comprising selecting the test composition if the test activity falls within a predetermined range of variance about the reference activity.

139. The method of claim 1, wherein the reference composition is a first production lot of a pharmaceutical composition comprising the known TLR ligand, and wherein the test composition is a second production lot of a pharmaceutical composition comprising the known TLR ligand.

140. The method of claim 137, wherein the reference composition is a first in-process lot of a composition comprising the known TLR ligand, and wherein the test composition is a second in-process lot of a composition comprising the known TLR ligand.

141. The method of claim 137, wherein the measuring the reference activity comprises contacting the reference composition with an isolated cell expressing a TLR responsive to the known TLR ligand, and wherein the measuring the test activity comprises contacting the test composition with the isolated cell expressing a TLR responsive to the known TLR ligand.

142. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand comprises an expression vector for the TLR responsive to the known TLR ligand.

143. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand naturally expresses the TLR responsive to the known TLR ligand.

144. The method of claim 141, wherein the isolated cell expressing the TLR responsive to the known TLR ligand is RPMI 8226.

145. The method of claim 137, wherein the measuring the reference activity and the measuring the test activity each comprise measuring signaling activity mediated by a TLR responsive to the known TLR ligand.

146. The method of claim 145, wherein the signaling activity is activity of a reporter construct under control of NF-κB response element.

147. The method of claim 145, wherein the signaling activity is activity of a reporter construct under control of interferon-stimulated response element (ISRE).

148. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IFN-α promoter.

149. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IFN-β promoter.

150. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-6 promoter.

151. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-8 promoter.

152. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of an IL-12 p40 promoter.

153. The method of claim 145, wherein the signaling activity is activity of a reporter gene under control of a RANTES promoter.

154. The method of claim 137, wherein the known TLR ligand is a TLR9 ligand.

155. The method of claim 137, wherein the known TLR ligand is a TLR3 ligand.

156. The method of claim 137, wherein the known TLR ligand is a TLR7 ligand.

157. The method of claim 137, wherein the known TLR ligand is a TLR8 ligand.

158. The method of claim 137, wherein the known TLR ligand is an immunostimulatory nucleic acid.

159. The method of claim 137, wherein the known TLR ligand is a CpG nucleic acid.

160. The method of claim 137, wherein the known TLR ligand is an immunoinhibitory nucleic acid.

161. A method for quality assessment of a test lot of a pharmaceutical product containing a known TLR9 ligand, comprising:

measuring a reference activity of a reference lot of a pharmaceutical product comprising a known TLR9 ligand, wherein the known TLR9 ligand is a nucleic acid molecule;

measuring a test activity of a test lot of a pharmaceutical product comprising the known TLR9 ligand;

comparing the test activity to the reference activity; and

rejecting the test lot if the test activity falls outside of a predetermined range of variance about the reference activity.

162. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence TCGTCGTTTTGTCGTTTTGTCGTT (SEQ ID NO:1).

163. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTGACGTTTTGTCGTT-3' (SEQ ID NO:139).

164. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTGTCGTTTTTTTCGA-3' (SEQ ID NO:140).

165. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTCGTCGTTTCGTCGTT-3' (SEQ ID NO:141).

166. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTCGTCGTTTTGTCGTT-3' (SEQ ID NO:142).

167. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTTCGGTCGTTTT-3' (SEQ ID NO:143).

168. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTTCGTGCGTTTTT-3' (SEQ ID NO:144).

169. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTCGTTTTCGGCGGCCGCCG-3' (SEQ ID NO:145).

170. The method of claim 161, wherein the known TLR9 ligand is an oligonucleotide comprising a base sequence 5'-TCGTC_GTTTTAC_GGCGCC_GTGCCG-3' (SEQ ID NO:146), wherein every internucleoside linkage is phosphorothioate except for those indicated by "_", which are phosphodiester.

171. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the cell is a Raji cell, a RAMOS cell, a Nalm cell, a THP-1 cell, or a KG-1 cell, and the TLR is TLR9.

172. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the cell is a Raji cell or a RAMOS cell, and the TLR is TLR7.

173. A screening method for identifying agonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell that expresses a TLR with a test compound and measuring a test level of TLR signaling activity,

wherein a test level that is positive is indicative of a test compound that is a TLR agonist, and

wherein the cell is a Raji cell, a RAMOS cell, a KG-1 cell, a Nalm-6 cell, a Jurkat cell, a Hela cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell or an NK-92 MI cell, and the TLR is TLR3.

174. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell, a Raji cell, a THP-1 cell, a Nalm cell and a KG-1 cell, and the TLR is TLR9.

175. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

wherein the cell is selected from the group consisting of a RPMI 8226 cell, a RAMOS cell and a Raji cell, and the TLR is TLR7.

175. A screening method for identifying antagonists of Toll-like receptor (TLR) signaling activity, comprising

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity,

contacting the cell with the positive reference compound and a test compound, and measuring a test level of TLR signaling activity,

wherein a test level that is less than a reference level is indicative of a test compound that is a TLR antagonist, and

wherein the cell is selected from the group consisting of a Raji cell, a RAMOS cell, a KG-1 cell, a Nalm-6 cell, a Jurkat cell, a Hela cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell and an NK-92 MI cell, and the TLR is TLR3.

176. A screening method for identifying an enhancer of a Toll-like receptor (TLR) agonist, comprising

contacting a cell with a positive reference compound and measuring a reference level of TLR signaling activity, and

contacting a cell with the positive reference compound and a test compound and measuring a test level of TLR signaling activity,

wherein the positive reference compound is a TLR agonist, and a test level that is greater than the reference level is indicative of a test compound that is an enhancer of a TLR agonist.

177. The method of claim 176, wherein the positive reference compound is an immunostimulatory nucleic acid.

178. The method of claim 176, wherein the positive reference compound is an imidazoquinoline compound.

180. The method of claim 176, wherein the cell is selected from the group consisting of a KG-1 cell, a Nalm-6 cell, a Raji cell, a RAMOS cell, a Jurkat cell, a Hela cell, a Hep-2 cell, an A549 cell, a Bewo cell, an NK-92 cell and an NK-92 MI cell, and the TLR is TLR3.

181. The method of claim 176, wherein the cell is selected from the group consisting of a KG-1 cell, a Nalm-6 cell, a Raji cell, an RPMI 8226 cell, a RAMOS cell, and a THP-1 cell, and the TLR is TLR9.

182. The method of claim 176, wherein the cell is selected from the group consisting of a Raji cell, an RPMI 8226 cell and a RAMOS cell, and the TLR is TLR7.

183. The method of claim 1, wherein the TLR is TLR7 or TLR9.

184. The method of claim 172-175 or 176, wherein the cell is unmodified.

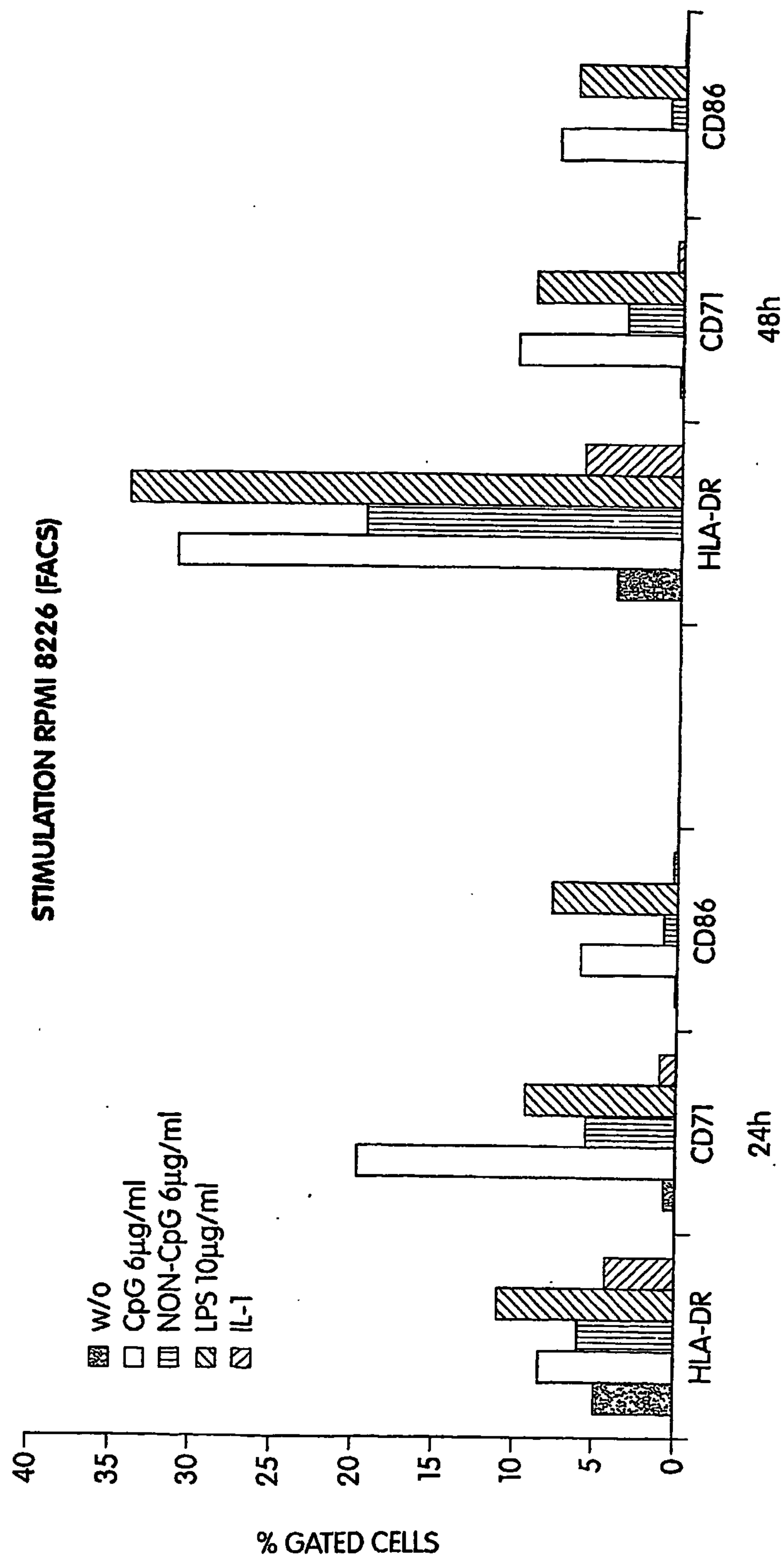

STIMULATION RPMI 8226 (FACS)
w/o
CpG 6µg/ml
NON-CpG 6µg/ml
LPS 10µg/ml
IL-1
% GATED CELLS
0
5
10
15
20
25
30
35
40
HLA-DR
CD71
CD86
24h
HLA-DR
CD71
CD86
48h

Fig. 1

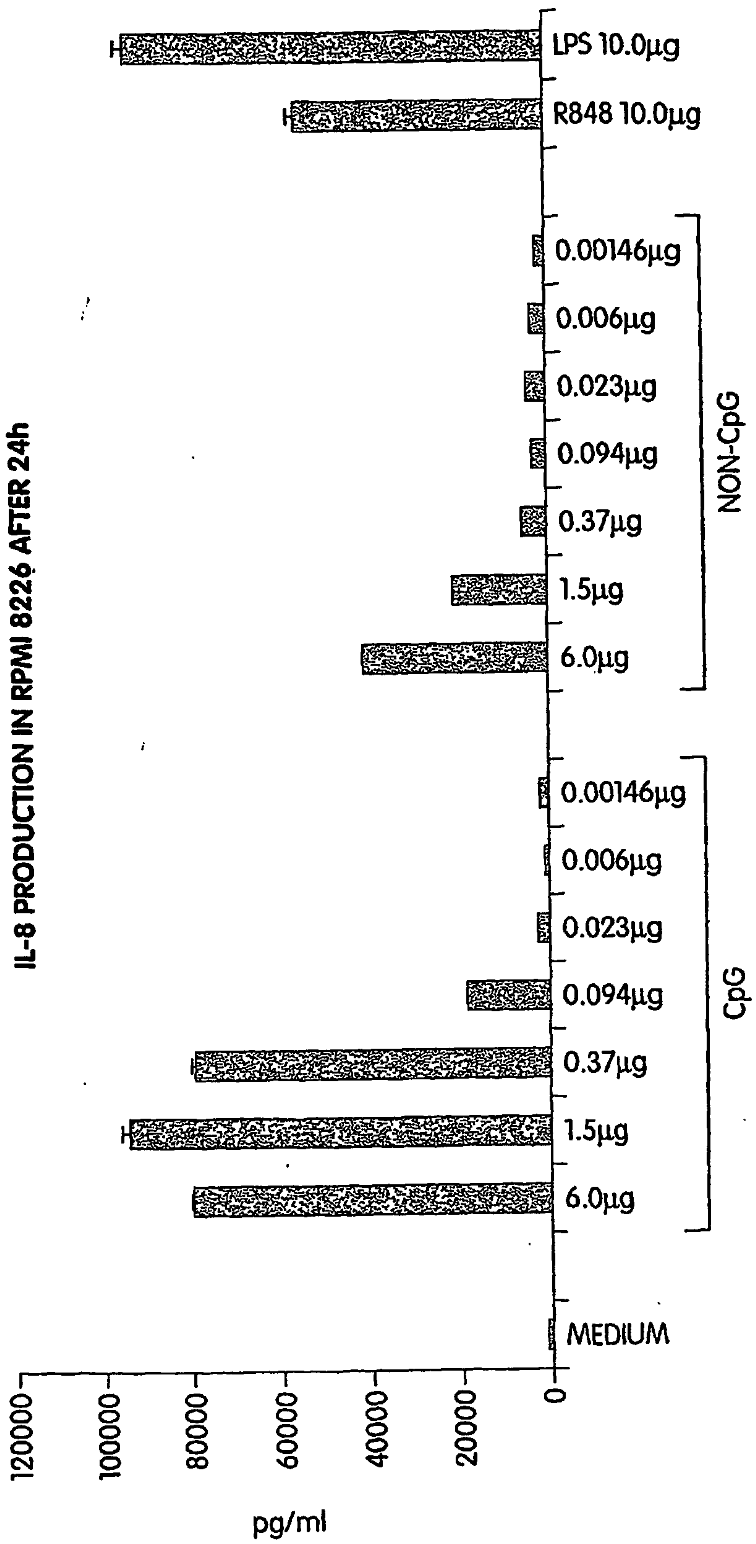

IL-8 PRODUCTION IN RPMI 8226 AFTER 24h
LPS 10.0µg
R848 10.0µg
0.00146µg
0.006µg
0.023µg
0.094µg
0.37µg
1.5µg
6.0µg
NON-CpG
0.00146µg
0.006µg
0.023µg
0.094µg
0.37µg
1.5µg
6.0µg
CpG
MEDIUM
120000
100000
80000
60000
40000
20000
0
pg/ml

Fig. 2

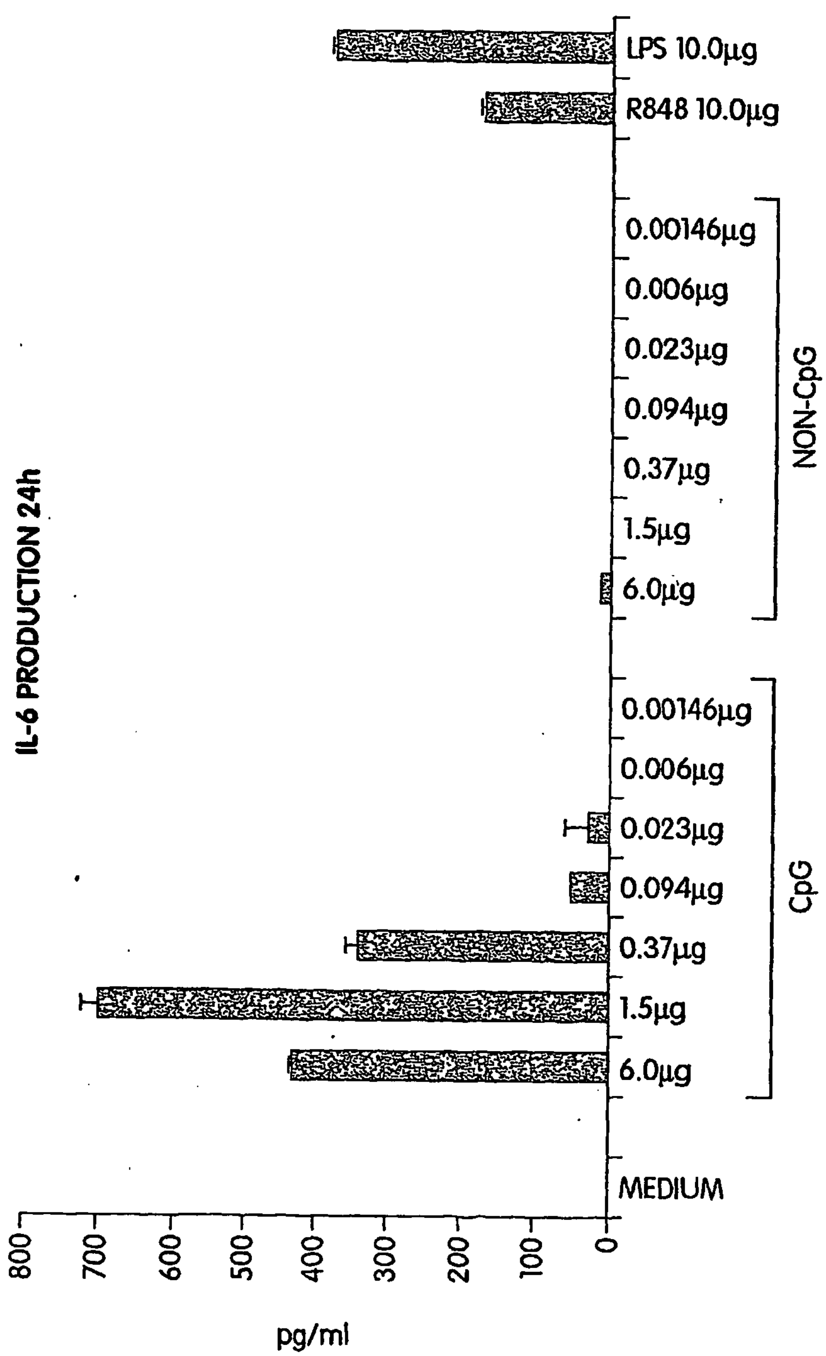

IL-6 PRODUCTION 24h
pg/ml
800
700
600
500
400
300
200
100
0
MEDIUM
6.0µg
1.5µg
0.37µg
0.094µg
0.023µg
0.006µg
0.00146µg
CpG
6.0µg
1.5µg
0.37µg
0.094µg
0.023µg
0.006µg
0.00146µg
NON-CpG
R848 10.0µg
LPS 10.0µg

Fig. 3

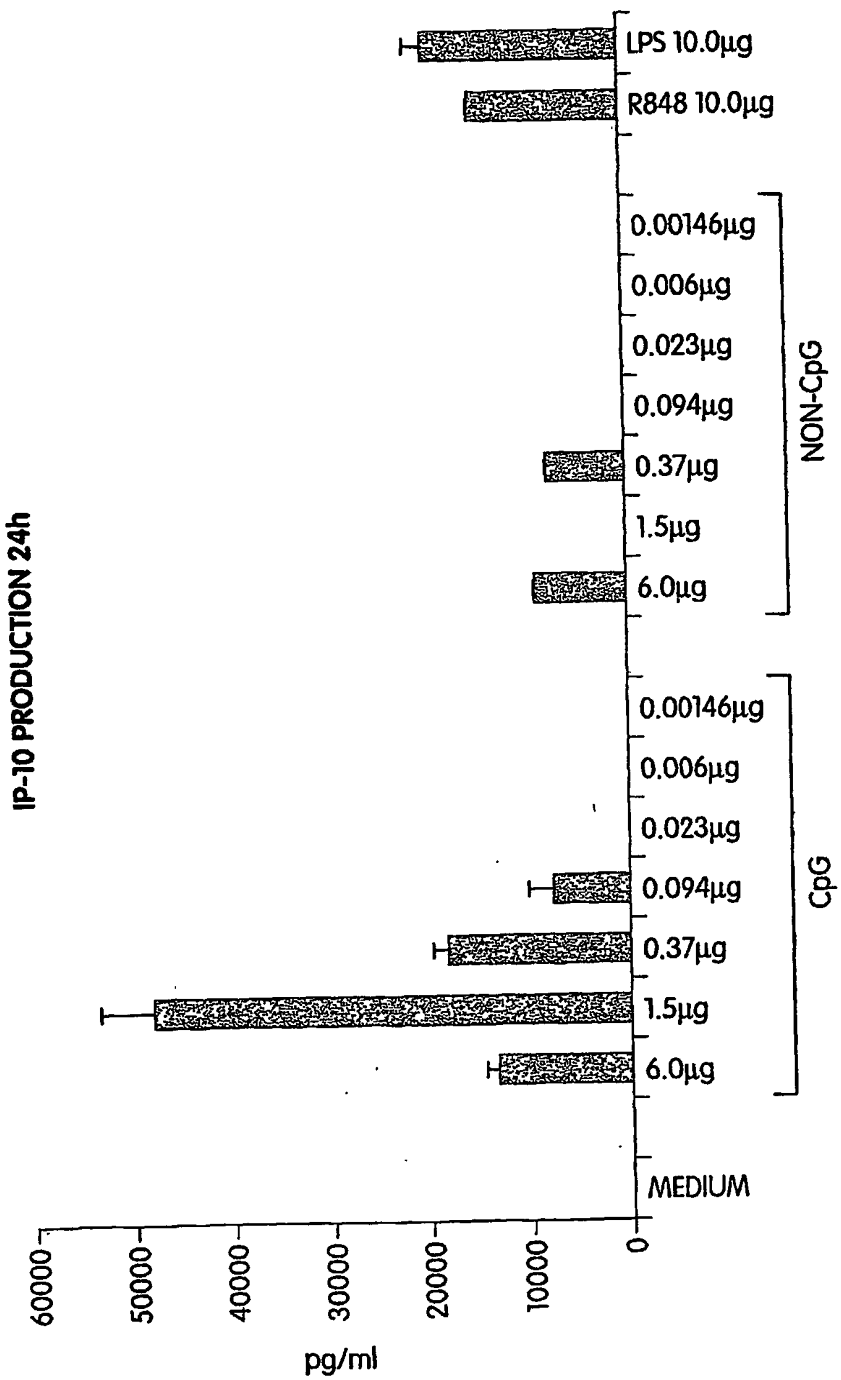

IP-10 PRODUCTION 24h
pg/ml
60000
50000
40000
30000
20000
10000
0
MEDIUM
6.0µg
1.5µg
0.37µg
0.094µg
0.023µg
0.006µg
0.00146µg
CpG
6.0µg
1.5µg
0.37µg
0.094µg
0.023µg
0.006µg
0.00146µg
NON-CpG
R848 10.0µg
LPS 10.0µg

Fig. 4

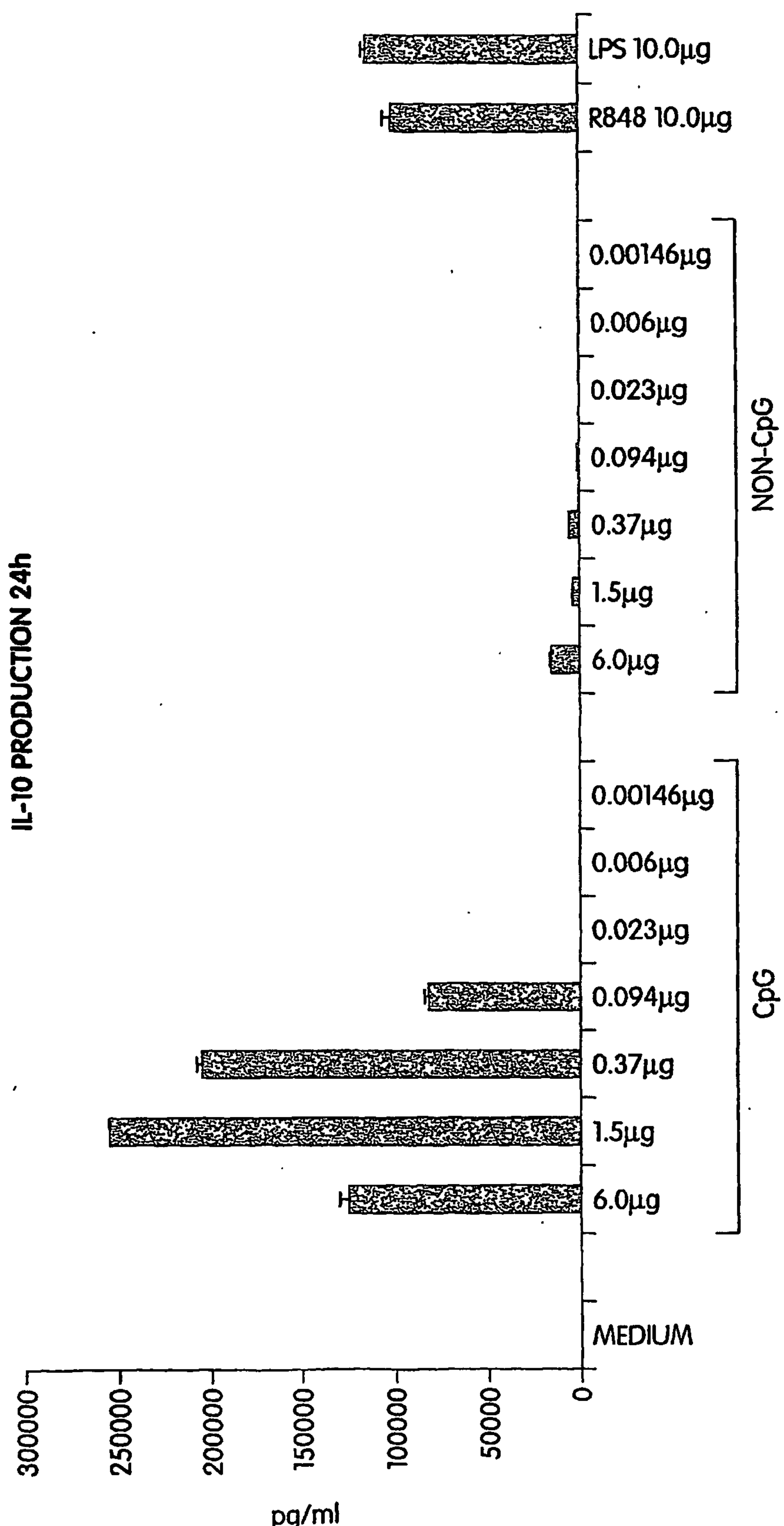

IL-10 PRODUCTION 24h
LPS 10.0μg
R848 10.0μg
0.00146μg
0.006μg
0.023μg
0.094μg
0.37μg
1.5μg
6.0μg
NON-CpG
0.00146μg
0.006μg
0.023μg
0.094μg
0.37μg
1.5μg
6.0μg
CpG
MEDIUM
300000
250000
200000
150000
100000
50000
0
pg/ml

Fig. 5

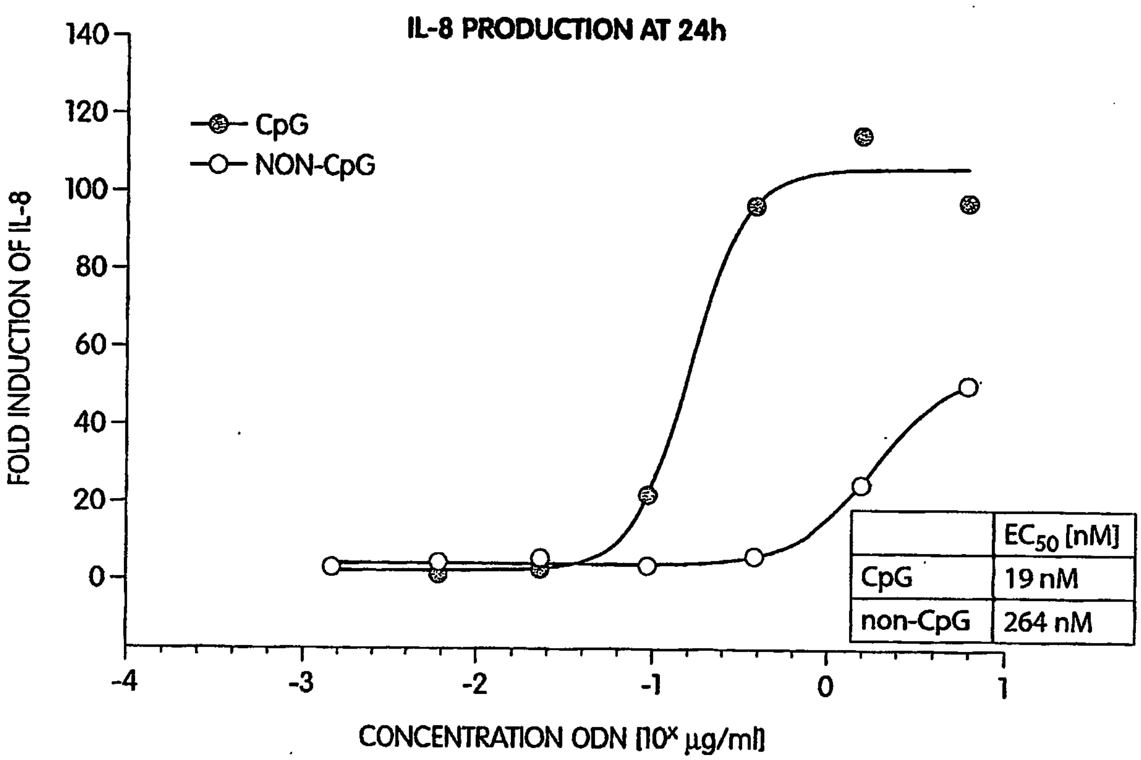

IL-8 PRODUCTION AT 24h
CpG
NON-CpG
FOLD INDUCTION OF IL-8
140
120
100
80
60
40
20
0
-4
-3
-2
-1
0
1
CONCENTRATION ODN [10ˣ μg/ml]
EC50 [nM]
CpG 19 nM
non-CpG 264 nM

Fig. 6

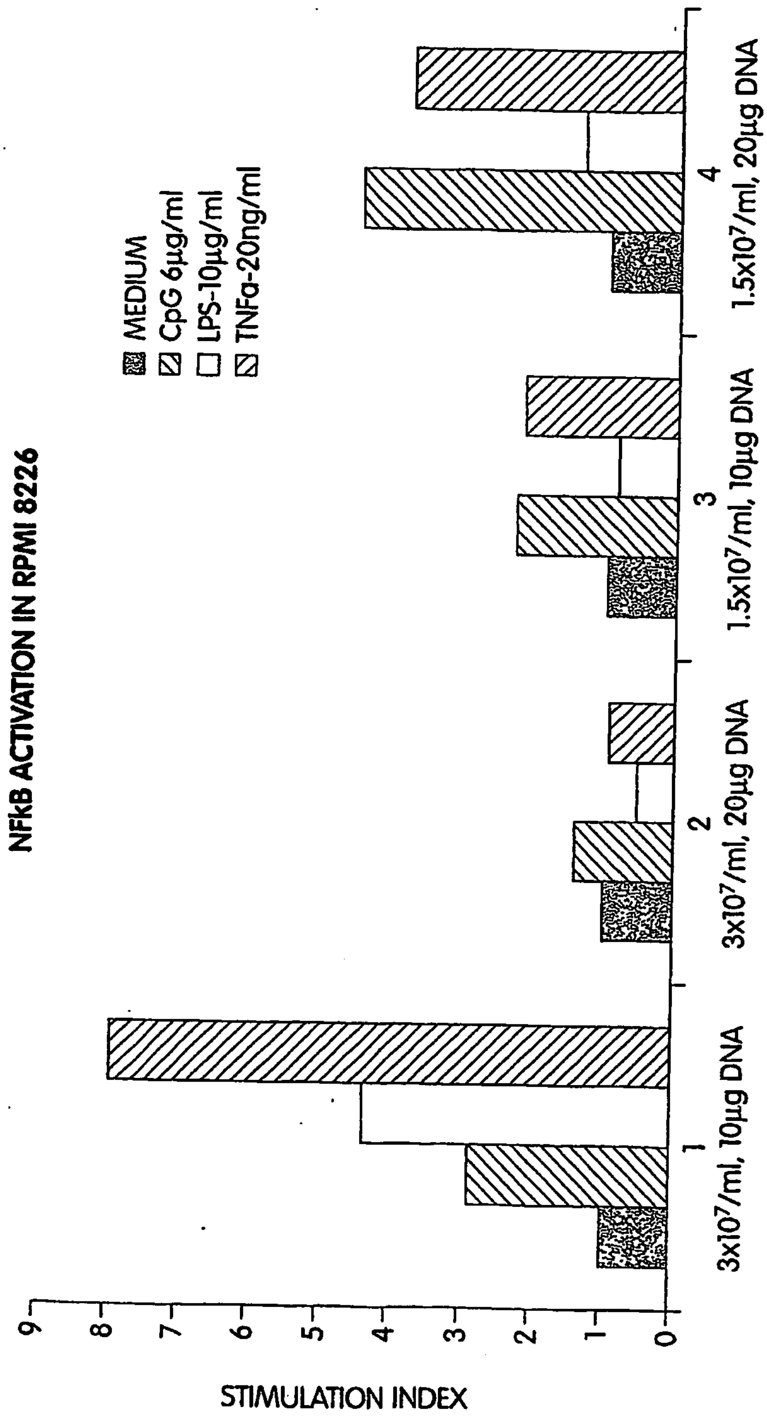

NFkB ACTIVATION IN RPMI 8226
MEDIUM
CpG 6μg/ml
LPS-10μg/ml
TNFa-20ng/ml
STIMULATION INDEX
0
1
2
3
4
5
6
7
8
9
1
3x10⁷/ml, 10μg DNA
2
3x10⁷/ml, 20μg DNA
3
1.5x10⁷/ml, 10μg DNA
4
1.5x10⁷/ml, 20μg DNA

Fig. 7

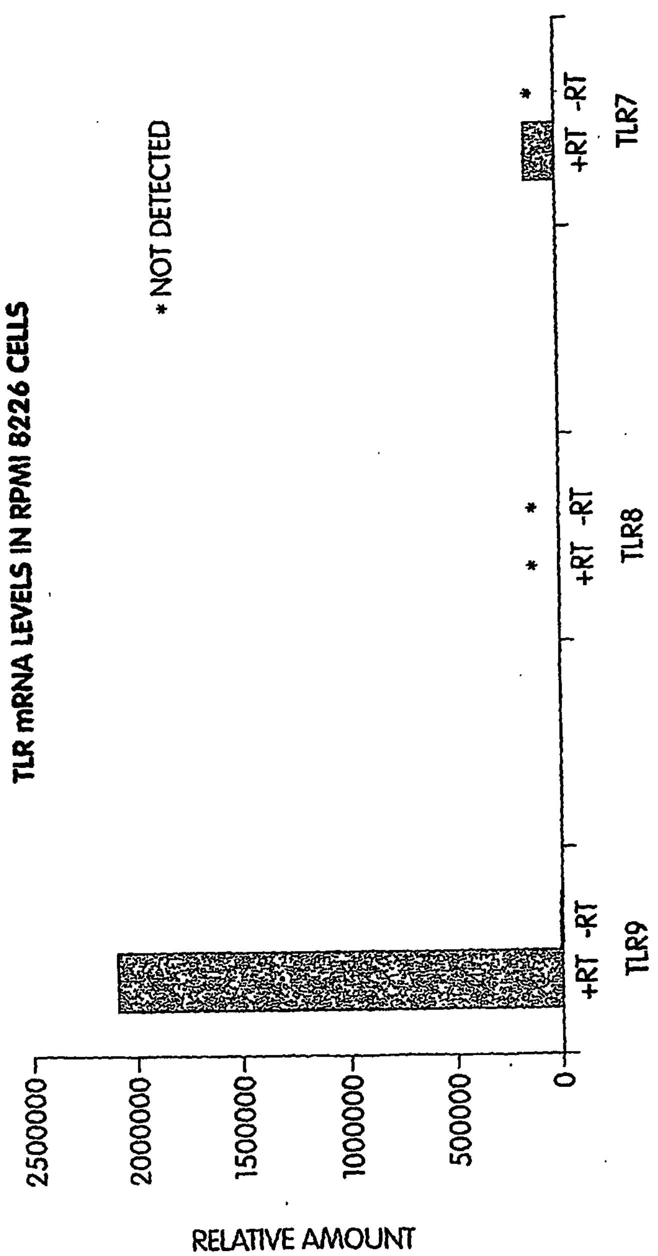

TLR mRNA LEVELS IN RPMI 8226 CELLS
* NOT DETECTED
RELATIVE AMOUNT
2500000
2000000
1500000
1000000
500000
0
+RT -RT
TLR9
+RT -RT
TLR8
+RT -RT
TLR7
*

Fig. 8

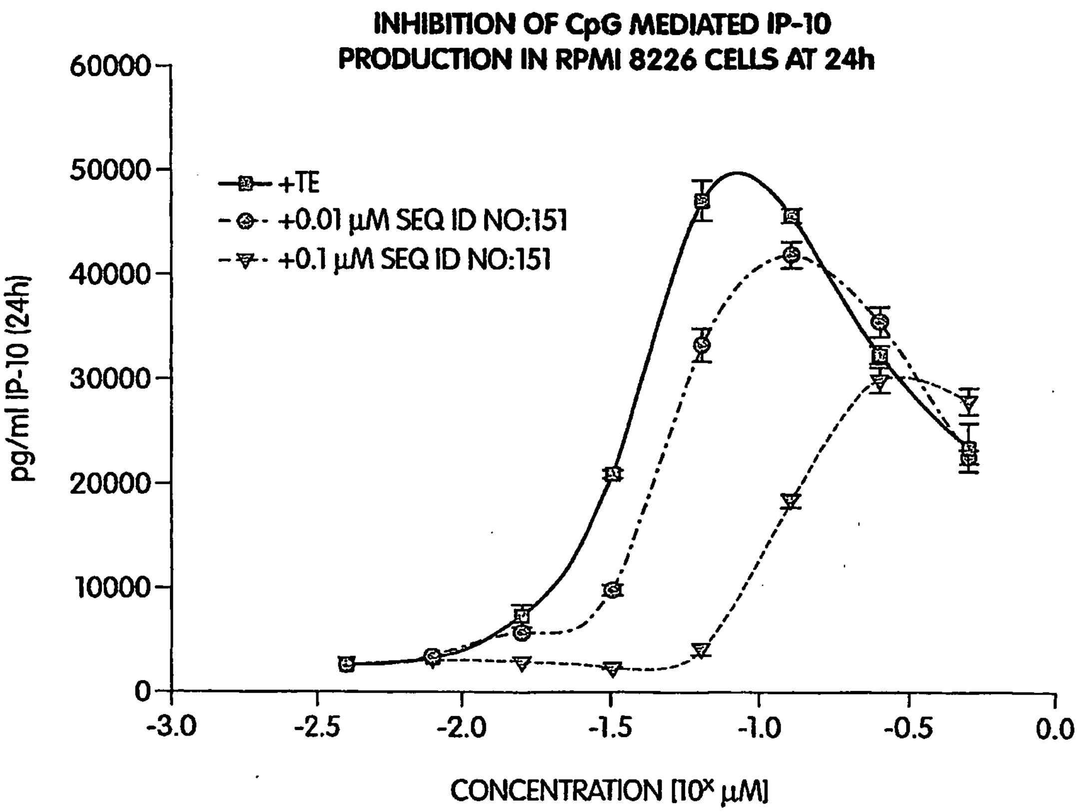

INHIBITION OF CpG MEDIATED IP-10
PRODUCTION IN RPMI 8226 CELLS AT 24h
+TE
+0.01 µM SEQ ID NO:151
+0.1 µM SEQ ID NO:151
pg/ml IP-10 (24h)
60000
50000
40000
30000
20000
10000
0
-3.0
-2.5
-2.0
-1.5
-1.0
-0.5
0.0
CONCENTRATION [10ˣ µM]

Fig. 9

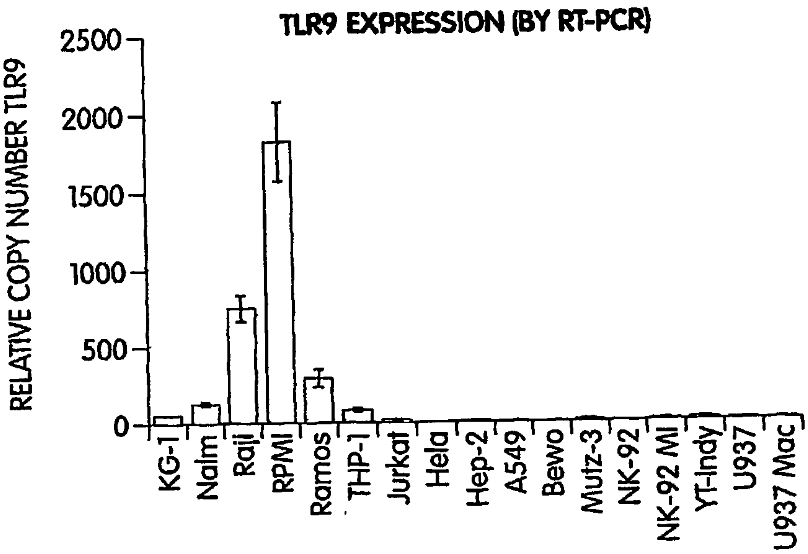

TLR9 EXPRESSION (BY RT-PCR)
RELATIVE COPY NUMBER TLR9
2500
2000
1500
1000
500
0
KG-1
Nalm
Raji
RPMI
Ramos
THP-1
Jurkat
Hela
Hep-2
A549
Bewo
Mutz-3
NK-92
NK-92 MI
YT-Indy
U937
U937 Mac

Fig. 10

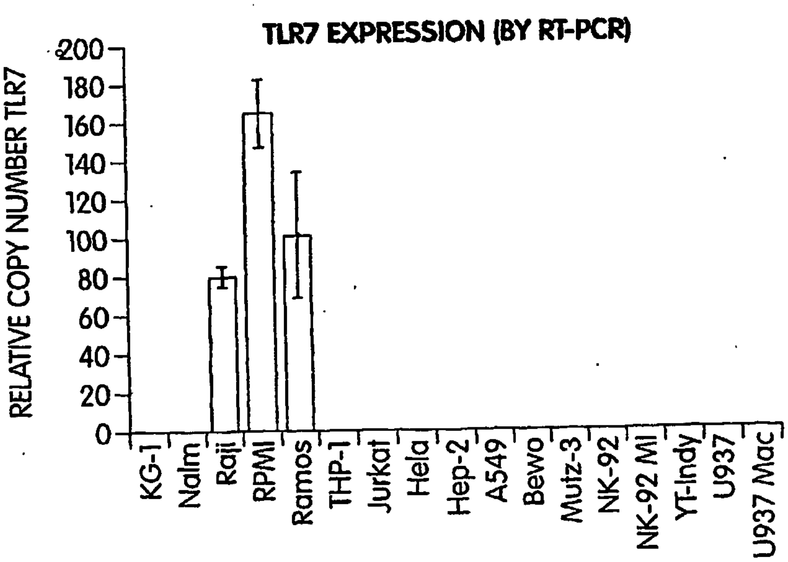

TLR7 EXPRESSION (BY RT-PCR)
RELATIVE COPY NUMBER TLR7
200
180
160
140
120
100
80
60
40
20
0
KG-1
Nalm
Raji
RPMI
Ramos
THP-1
Jurkat
Hela
Hep-2
A549
Bewo
Mutz-3
NK-92
NK-92 MI
YT-Indy
U937
U937 Mac

Fig. 11

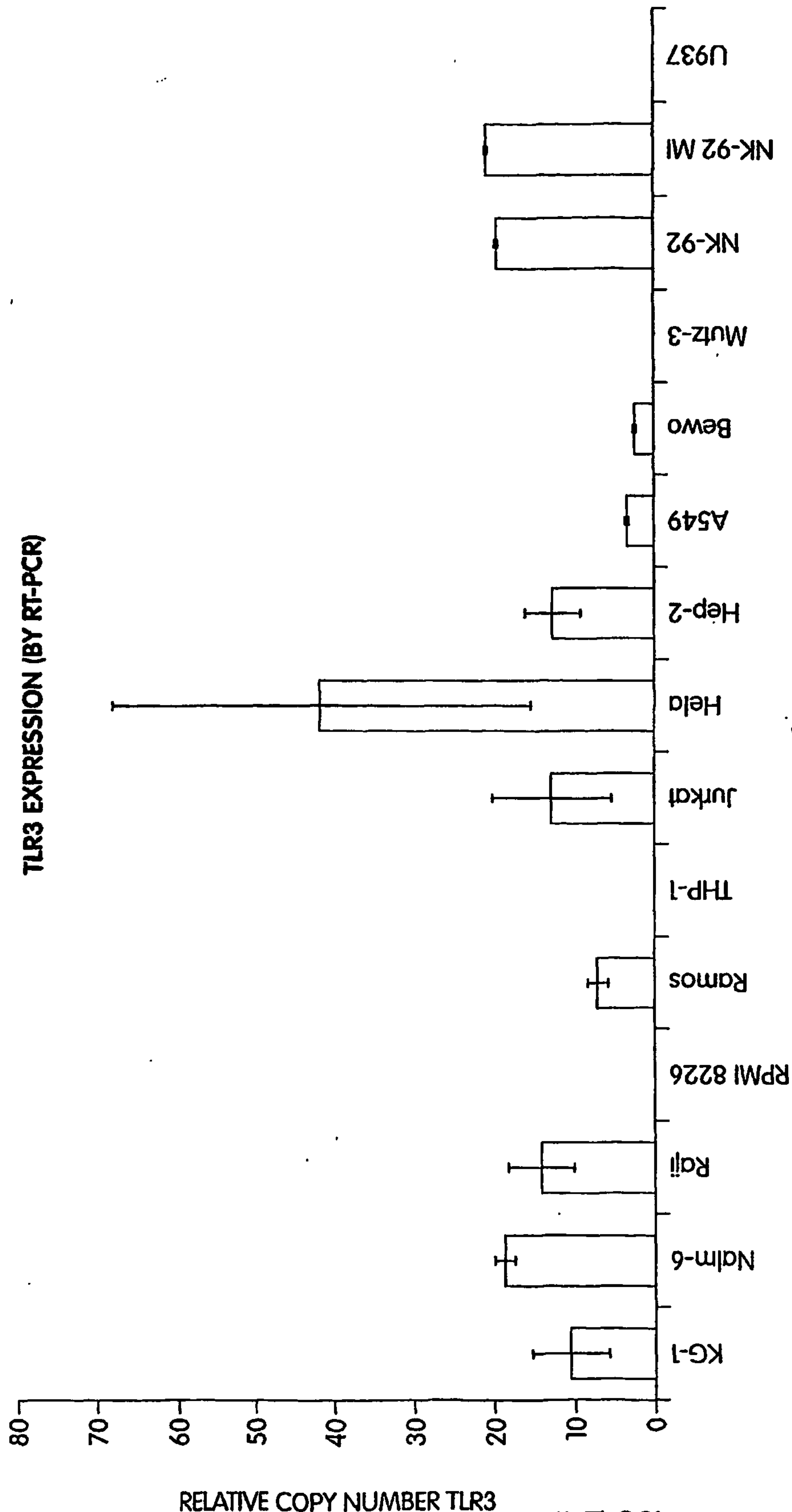

TLR3 EXPRESSION (BY RT-PCR)
RELATIVE COPY NUMBER TLR3
0
10
20
30
40
50
60
70
80
KG-1
Nalm-6
Raji
RPMI 8226
Ramos
THP-1
Jurkat
Hela
Hep-2
A549
Bewo
Mutz-3
NK-92
NK-92 MI
U937

Fig. 12

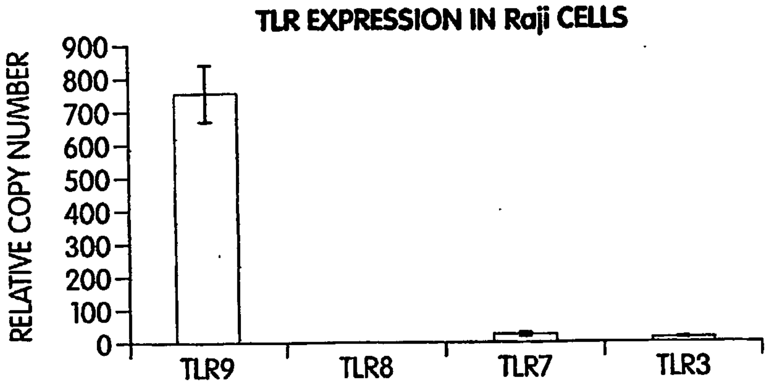

TLR EXPRESSION IN Raji CELLS
RELATIVE COPY NUMBER
900
800
700
600
500
400
300
200
100
0
TLR9
TLR8
TLR7
TLR3

Fig. 13

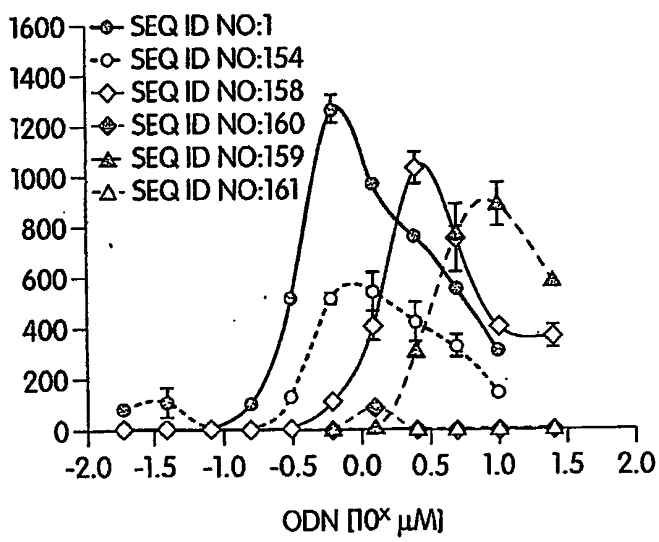

SEQ ID NO:1
SEQ ID NO:154
SEQ ID NO:158
SEQ ID NO:160
SEQ ID NO:159
SEQ ID NO:161
1600
1400
1200
1000
800
600
400
200
0
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
ODN [10^x μM]

Fig. 14

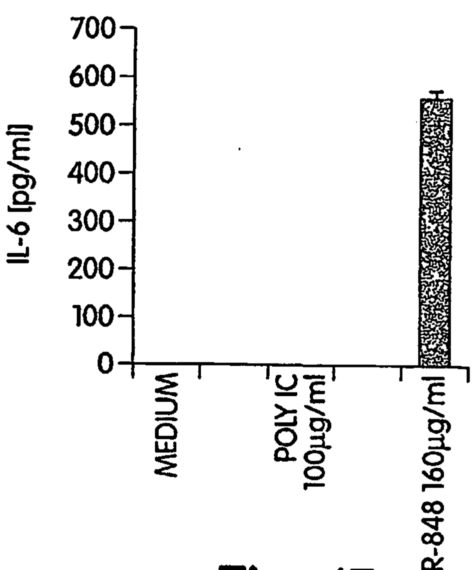


Fig. 15

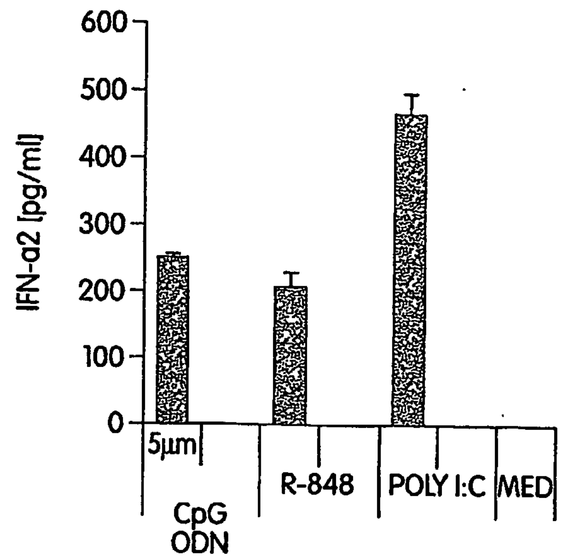


Fig. 16

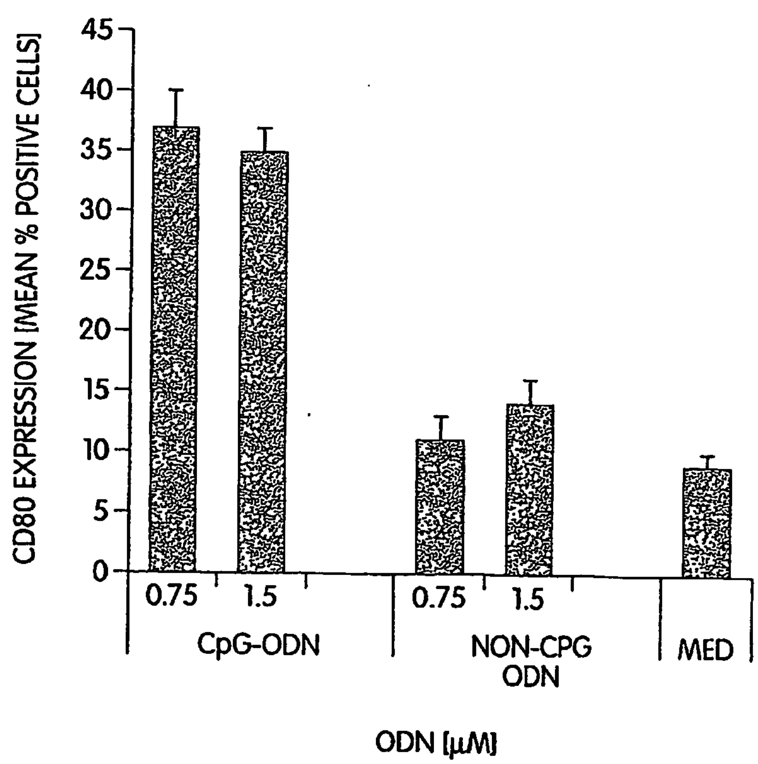
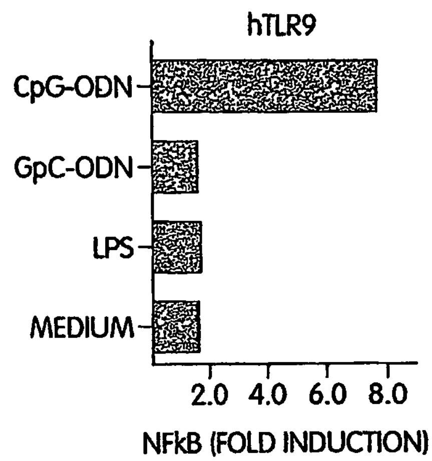


Fig. 17



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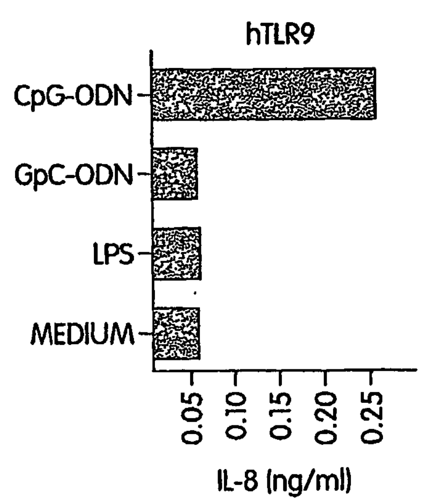
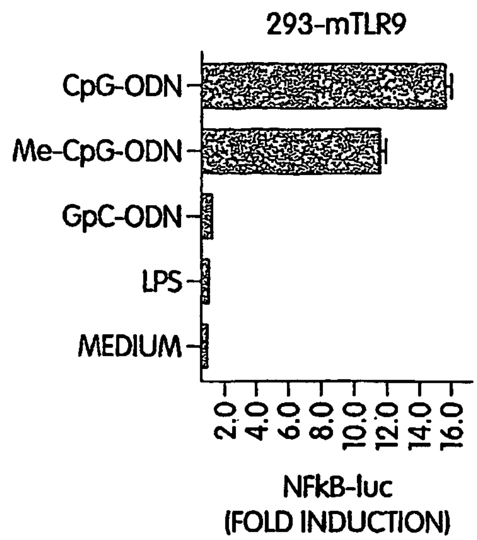


Fig. 18B



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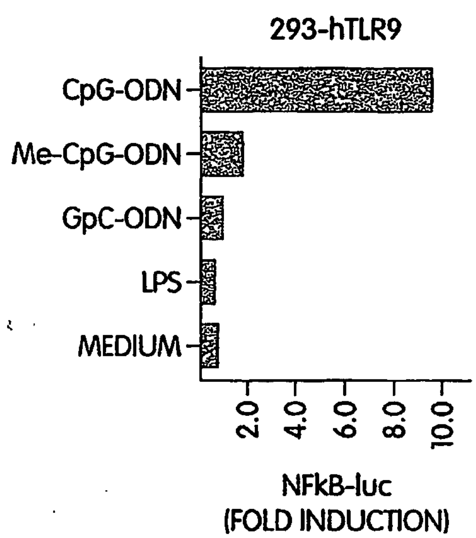

Fig. 20

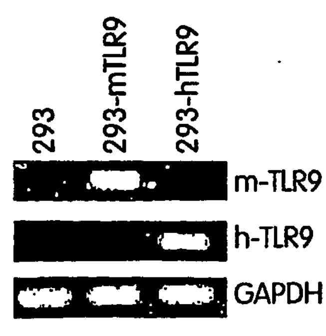

Fig. 21

SEQUENCE LISTING

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COLEY PHARMACEUTICAL GROUP INC.

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Ser Tyr Leu Cys Asp Ser Pro Pro Arg Leu His Gly His Arg Leu Gln
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Asp Ala Arg Pro Ser Val Leu Glu Cys His Gln Ala Ala Leu Val Ser
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Glu Val Ala Asp Cys Ser His Leu Lys Leu Thr Gln Val Pro Asp Asp
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Leu Pro Thr Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu Arg
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Arg Leu Pro Ala Ala Asn Phe Thr Arg Tyr Ser Gln Leu Thr Ser Leu

65 70 75 80
Asp Val Gly Phe Asn Thr Ile Ser Lys Leu Glu Pro Glu Leu Cys Gln
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Lys Leu Pro Met Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu Ser
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Gln Leu Ser Asp Lys Thr Phe Ala Phe Cys Thr Asn Leu Thr Glu Leu
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His Leu Met Ser Asn Ser Ile Gln Lys Ile Lys Asn Asn Pro Phe Val
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Lys Gln Lys Asn Leu Ile Thr Leu Asp Leu Ser His Asn Gly Leu Ser
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Ser Thr Lys Leu Gly Thr Gln Val Gln Leu Glu Asn Leu Gln Glu Leu
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195 200 205

Ile Lys Glu Phe Ser Pro Gly Cys Phe His Ala Ile Gly Arg Leu Phe
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Gly Leu Phe Leu Asn Asn Val Gln Leu Gly Pro Ser Leu Thr Glu Lys
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Leu Cys Leu Glu Leu Ala Asn Thr Ser Ile Arg Asn Leu Ser Leu Ser
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260 265 270

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Val Gly Asn Asp Ser Phe Ala Trp Leu Pro Gln Leu Glu Tyr Phe Phe
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Ser Ile Ser Leu Ala Ser Leu Pro Lys Ile Asp Asp Phe Ser Phe Gln
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Trp Leu Lys Cys Leu Glu His Leu Asn Met Glu Asp Asn Asp Ile Pro
355 360 365

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385 390 395 400

Phe Val Ser Leu Ala His Ser Pro Leu His Ile Leu Asn Leu Thr Lys

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Gly Gln Glu Trp Arg Gly Leu Glu Asn Ile Phe Glu Ile Tyr Leu Ser
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Tyr Asn Lys Tyr Leu Gln Leu Thr Arg Asn Ser Phe Ala Leu Val Pro
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Gln Val Ser Leu Lys Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr Ser
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Ser His Tyr Leu Cys Asn Thr Pro Pro His Tyr His Gly Phe Pro Val
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Arg Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu Leu
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Phe Phe Met Ile Asn Thr Ser Ile Leu Leu Ile Phe Ile Phe Ile Val
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Ser Val His Arg Val Leu Gly Phe Lys Glu Ile Asp Arg Gln Thr Glu

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Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe Val
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Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Lys Arg Phe Lys Val
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His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile Ile
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Leu Val Phe Leu Glu Glu Ile Pro Asp Tyr Lys Leu Asn His Ala Leu
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Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp Pro
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35 40 45

Asp Leu Pro Ser Asn Ile Thr Val Leu Asn Leu Thr His Asn Gln Leu
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Arg Arg Leu Pro Pro Thr Asn Phe Thr Arg Tyr Ser Gln Leu Ala Ile
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Leu Asp Ala Gly Phe Asn Ser Ile Ser Lys Leu Glu Pro Glu Leu Cys
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Gln Ile Leu Pro Leu Leu Lys Val Leu Asn Leu Gln His Asn Glu Leu
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Ser Gln Ile Ser Asp Gln Thr Phe Val Phe Cys Thr Asn Leu Thr Glu
115 120 125

Leu Asp Leu Met Ser Asn Ser Ile His Lys Ile Lys Ser Asn Pro Phe
130 135 140

Lys Asn Gln Lys Asn Leu Ile Lys Leu Asp Leu Ser His Asn Gly Leu
145 150 155 160

Ser Ser Thr Lys Leu Gly Thr Gly Val Gln Leu Glu Asn Leu Gln Glu
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Leu Leu Leu Ala Lys Asn Lys Ile Leu Ala Leu Arg Ser Glu Glu Leu
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Glu Phe Leu Gly Asn Ser Ser Leu Arg Lys Leu Asp Leu Ser Ser Asn
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Pro Leu Lys Glu Phe Ser Pro Gly Cys Phe Gln Thr Ile Gly Lys Leu
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Phe Ala Leu Leu Leu Asn Asn Ala Gln Leu Asn Pro His Leu Thr Glu
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Lys Leu Cys Trp Glu Leu Ser Asn Thr Ser Ile Gln Asn Leu Ser Leu
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Ala Asn Asn Gln Leu Leu Ala Thr Ser Glu Ser Thr Phe Ser Gly Leu
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Lys Trp Thr Asn Leu Thr Gln Leu Asp Leu Ser Tyr Asn Asn Leu His
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Gly Leu Ser Asn Leu Arg Tyr Leu Ser Leu Lys Arg Ala Phe Thr Lys
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Gln Trp Leu Lys Tyr Leu Glu Tyr Leu Asn Met Asp Asp Asn Asn Ile
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Pro Ser Thr Lys Ser Asn Thr Phe Thr Gly Leu Val Ser Leu Lys Tyr
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Thr Phe Val Ser Leu Ala His Ser Pro Leu Leu Thr Leu Asn Leu Thr
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Lys Asn His Ile Ser Lys Ile Ala Asn Gly Thr Phe Ser Trp Leu Gly
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Gln Leu Arg Ile Leu Asp Leu Gly Leu Asn Glu Ile Glu Gln Lys Leu
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Ser Gly Gln Glu Trp Arg Gly Leu Arg Asn Ile Phe Glu Ile Tyr Leu
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Ser Tyr Asn Lys Tyr Leu Gln Leu Ser Thr Ser Ser Phe Ala Leu Val
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Pro Ser Leu Gln Arg Leu Met Leu Arg Arg Val Ala Leu Lys Asn Val

485 490 495

Asp Ile Ser Pro Ser Pro Phe Arg Pro Leu Arg Asn Leu Thr Ile Leu
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Asp Leu Ser Asn Asn Asn Ile Ala Asn Ile Asn Glu Asp Leu Leu Glu
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Gly Leu Glu Asn Leu Glu Ile Leu Asp Phe Gln His Asn Asn Leu Ala
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Arg Leu Trp Lys Arg Ala Asn Pro Gly Gly Pro Val Asn Phe Leu Lys
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Gly Leu Ser His Leu His Ile Leu Asn Leu Glu Ser Asn Gly Leu Asp
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Glu Ile Pro Val Gly Val Phe Lys Asn Leu Phe Glu Leu Lys Ser Ile
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Asn Leu Gly Leu Asn Asn Leu Asn Lys Leu Glu Pro Phe Ile Phe Asp
595 600 605

Asp Gln Thr Ser Leu Arg Ser Leu Asn Leu Gln Lys Asn Leu Ile Thr
610 615 620

Ser Val Glu Lys Asp Val Phe Gly Pro Pro Phe Gln Asn Leu Asn Ser
625 630 635 640

Leu Asp Met Arg Phe Asn Pro Phe Asp Cys Thr Cys Glu Ser Ile Ser
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Trp Phe Val Asn Trp Ile Asn Gln Thr His Thr Asn Ile Phe Glu Leu
660 665 670

Ser Thr His Tyr Leu Cys Asn Thr Pro His His Tyr Tyr Gly Phe Pro
675 680 685

Leu Lys Leu Phe Asp Thr Ser Ser Cys Lys Asp Ser Ala Pro Phe Glu
690 695 700

Leu Leu Phe Ile Ile Ser Thr Ser Met Leu Leu Val Phe Ile Leu Val
705 710 715 720

Val Leu Leu Ile His Ile Glu Gly Trp Arg Ile Ser Phe Tyr Trp Asn
725 730 735

Val Ser Val His Arg Ile Leu Gly Phe Lys Glu Ile Asp Thr Gln Ala
740 745 750

Glu Gln Phe Glu Tyr Thr Ala Tyr Ile Ile His Ala His Lys Asp Arg
755 760 765

Asp Trp Val Trp Glu His Phe Ser Pro Met Glu Glu Gln Asp Gln Ser
770 775 780

Leu Lys Phe Cys Leu Glu Glu Arg Asp Phe Glu Ala Gly Val Leu Gly
785 790 795 800

Leu Glu Ala Ile Val Asn Ser Ile Lys Arg Ser Arg Lys Ile Ile Phe
805 810 815

Val Ile Thr His His Leu Leu Lys Asp Pro Leu Cys Arg Arg Phe Lys

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Val His His Ala Val Gln Gln Ala Ile Glu Gln Asn Leu Asp Ser Ile
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Leu Cys Leu Arg Arg Gly Met Phe Lys Ser His Cys Ile Leu Asn Trp
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Pro Val Gln Lys Glu Arg Ile Asn Ala Phe His His Lys Leu Gln Val
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aaaacttcct tccagatatc ttcacagagc tgagaaactt gaccttcctg gacctctctc 1800

agtgtcaact ggagcagttg tctccaacag catttaactc actctccagt cttcaggtac 1860

taaatatgag ccacaacaac ttcttttcat tggatacgtt tccttataag tgtctgaact 1920

ccctccaggt tcttgattac agtctcaatc acataatgac ttccaaaaaa caggaactac 1980

agcattttcc aagtagtcta gctttcttaa atcttactca gaatgacttt gcttgtactt 2040

gtgaacacca gagtttcctg caatggatca aggaccagag gcagctcttg gtggaagttg 2100

aacgaatgga atgtgcaaca ccttcagata agcagggcat gcctgtgctg agtttgaata 2160

tcacctgtca gatgaataag accatcattg gtgtgtcggt cctcagtgtg cttgtagtat 2220

ctgttgtagc agttctggtc tataagttct attttcacct gatgcttctt gctggctgca 2280

taaagtatgg tagaggtgaa aacatctatg atgcctttgt tatctactca agccaggatg 2340

aggactgggt aaggaatgag ctagtaaaga atttagaaga aggggtgcct ccatttcagc 2400

tctgccttca ctacagagac tttattcccg gtgtggccat tgctgccaac atcatccatg 2460

aaggtttcca taaaagccga aaggtgattg ttgtggtgtc ccagcacttc atccagagcc 2520

gctggtgtat ctttgaatat gagattgctc agacctggca gtttctgagc agtcgtgctg 2580

gtatcatctt cattgtcctg cagaaggtgg agaagaccct gctcaggcag caggtggagc 2640

tgtaccgcct tctcagcagg aacacttacc tggagtggga ggacagtgtc ctggggcggc 2700

acatcttctg gagacgactc agaaaagccc tgctggatgg taaatcatgg aatccagaag 2760

gaacagtggg tacaggatgc aattggcagg aagcaacatc tatctgaaga ggaaaaataa 2820

aaacctcctg aggcatttct tgcccagctg ggtccaacac ttgttcagtt aataagtatt 2880

aaatgctgcc acatgtcagg ccttatgcta agggtgagta attccatggt gcactagata 2940

tgcagggctg ctaatctcaa ggagcttcca gtgcagaggg aataaatgct agactaaaat 3000

acagagtctt ccaggtgggc atttcaacca actcagtcaa ggaacccatg acaaagaaag 3060

tcatttcaac tcttacctca tcaagttgaa taaagacaga gaaaacagaa agagacattg 3120

ttcttttcct gagtcttttg aatggaaatt gtattatgtt atagccatca taaaaccatt 3180

ttggtagttt tgactgaact gggtgttcac tttttccttt ttgattgaat acaatttaaa 3240

ttctacttga tgactgcagt cgtcaagggg ctcctgatgc aagatgcccc ttccatttta 3300

agtctgtctc cttacagagg ttaaagtcta gtggctaatt cctaaggaaa cctgattaac 3360

acatgctcac aaccatcctg gtcattctcg agcatgttct attttttaac taatcacccc 3420

tgatatattt ttattttttat atatccagtt ttcatttttt tacgtcttgc ctataagcta 3480

atatcataaa taaggttgtt taagacgtgc ttcaaatatc catattaacc actatttttc 3540

aaggaagtat ggaaaagtac actctgtcac tttgtcactc gatgtcattc caaagttatt 3600

gcctactaag taatgactgt catgaaagca gcattgaaat aatttgttta aagggggcac 3660

tcttttaaac gggaagaaaa tttccgcttc ctggtcttat catggacaat ttgggctaga 3720

ggcaggaagg aagtgggatg acctcaggag gtcacctttt cttgattcca gaaacatatg 3780

ggctgataaa cccggggtga cctcatgaaa tgagttgcag cagaagttta tttttttcag 3840

aacaagtgat gtttgatgga cctctgaatc tctttaggga gacacagatg gctgggatcc 3900

ctcccctgta cccttctcac tgccaggaga acta 3934

<210> 16
<211> 839
<212> PRT
<213> Homo sapiens

<400> 16

Met Met Ser Ala Ser Arg Leu Ala Gly Thr Leu Ile Pro Ala Met Ala
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Phe Leu Ser Cys Val Arg Pro Glu Ser Trp Glu Pro Cys Val Glu Val
20 25 30

Val Pro Asn Ile Thr Tyr Gln Cys Met Glu Leu Asn Phe Tyr Lys Ile
35 40 45

Pro Asp Asn Leu Pro Phe Ser Thr Lys Asn Leu Asp Leu Ser Phe Asn
50 55 60

Pro Leu Arg His Leu Gly Ser Tyr Ser Phe Phe Ser Phe Pro Glu Leu
65 70 75 80

Gln Val Leu Asp Leu Ser Arg Cys Glu Ile Gln Thr Ile Glu Asp Gly
85 90 95

Ala Tyr Gln Ser Leu Ser His Leu Ser Thr Leu Ile Leu Thr Gly Asn
100 105 110

Pro Ile Gln Ser Leu Ala Leu Gly Ala Phe Ser Gly Leu Ser Ser Leu
115 120 125

Gln Lys Leu Val Ala Val Glu Thr Asn Leu Ala Ser Leu Glu Asn Phe
130 135 140

Pro Ile Gly His Leu Lys Thr Leu Lys Glu Leu Asn Val Ala His Asn
145 150 155 160

Leu Ile Gln Ser Phe Lys Leu Pro Glu Tyr Phe Ser Asn Leu Thr Asn
165 170 175

Leu Glu His Leu Asp Leu Ser Ser Asn Lys Ile Gln Ser Ile Tyr Cys
180 185 190

Thr Asp Leu Arg Val Leu His Gln Met Pro Leu Leu Asn Leu Ser Leu
195 200 205

Asp Leu Ser Leu Asn Pro Met Asn Phe Ile Gln Pro Gly Ala Phe Lys
210 215 220

Glu Ile Arg Leu His Lys Leu Thr Leu Arg Asn Asn Phe Asp Ser Leu
225 230 235 240

Asn Val Met Lys Thr Cys Ile Gln Gly Leu Ala Gly Leu Glu Val His
245 250 255

Arg Leu Val Leu Gly Glu Phe Arg Asn Glu Gly Asn Leu Glu Lys Phe
260 265 270

Asp Lys Ser Ala Leu Glu Gly Leu Cys Asn Leu Thr Ile Glu Glu Phe
275 280 285

Arg Leu Ala Tyr Leu Asp Tyr Tyr Leu Asp Asp Ile Ile Asp Leu Phe
290 295 300

Asn Cys Leu Thr Asn Val Ser Ser Phe Ser Leu Val Ser Val Thr Ile
305 310 315 320

Glu Arg Val Lys Asp Phe Ser Tyr Asn Phe Gly Trp Gln His Leu Glu
325 330 335

Leu Val Asn Cys Lys Phe Gly Gln Phe Pro Thr Leu Lys Leu Lys Ser
340 345 350

Leu Lys Arg Leu Thr Phe Thr Ser Asn Lys Gly Gly Asn Ala Phe Ser
355 360 365

Glu Val Asp Leu Pro Ser Leu Glu Phe Leu Asp Leu Ser Arg Asn Gly
370 375 380

Leu Ser Phe Lys Gly Cys Cys Ser Gln Ser Asp Phe Gly Thr Thr Ser
385 390 395 400

Leu Lys Tyr Leu Asp Leu Ser Phe Asn Gly Val Ile Thr Met Ser Ser
405 410 415

Asn Phe Leu Gly Leu Glu Gln Leu Glu His Leu Asp Phe Gln His Ser

420 425 430
Asn Leu Lys Gln Met Ser Glu Phe Ser Val Phe Leu Ser Leu Arg Asn
435 440 445

Leu Ile Tyr Leu Asp Ile Ser His Thr His Thr Arg Val Ala Phe Asn
450 455 460

Gly Ile Phe Asn Gly Leu Ser Ser Leu Glu Val Leu Lys Met Ala Gly
465 470 475 480

Asn Ser Phe Gln Glu Asn Phe Leu Pro Asp Ile Phe Thr Glu Leu Arg
485 490 495

Asn Leu Thr Phe Leu Asp Leu Ser Gln Cys Gln Leu Glu Gln Leu Ser
500 505 510

Pro Thr Ala Phe Asn Ser Leu Ser Ser Leu Gln Val Leu Asn Met Ser
515 520 525

His Asn Asn Phe Phe Ser Leu Asp Thr Phe Pro Tyr Lys Cys Leu Asn
530 535 540

Ser Leu Gln Val Leu Asp Tyr Ser Leu Asn His Ile Met Thr Ser Lys
545 550 555 560

Lys Gln Glu Leu Gln His Phe Pro Ser Ser Leu Ala Phe Leu Asn Leu
565 570 575

Thr Gln Asn Asp Phe Ala Cys Thr Cys Glu His Gln Ser Phe Leu Gln
580 585 590

Trp Ile Lys Asp Gln Arg Gln Leu Leu Val Glu Val Glu Arg Met Glu
595 600 605

Cys Ala Thr Pro Ser Asp Lys Gln Gly Met Pro Val Leu Ser Leu Asn
610 615 620

Ile Thr Cys Gln Met Asn Lys Thr Ile Ile Gly Val Ser Val Leu Ser
625 630 635 640

Val Leu Val Val Ser Val Val Ala Val Leu Val Tyr Lys Phe Tyr Phe
645 650 655

His Leu Met Leu Leu Ala Gly Cys Ile Lys Tyr Gly Arg Gly Glu Asn
660 665 670

Ile Tyr Asp Ala Phe Val Ile Tyr Ser Ser Gln Asp Glu Asp Trp Val
675 680 685

Arg Asn Glu Leu Val Lys Asn Leu Glu Glu Gly Val Pro Pro Phe Gln
690 695 700

Leu Cys Leu His Tyr Arg Asp Phe Ile Pro Gly Val Ala Ile Ala Ala
705 710 715 720

Asn Ile Ile His Glu Gly Phe His Lys Ser Arg Lys Val Ile Val Val
725 730 735

Val Ser Gln His Phe Ile Gln Ser Arg Trp Cys Ile Phe Glu Tyr Glu
740 745 750

Ile Ala Gln Thr Trp Gln Phe Leu Ser Ser Arg Ala Gly Ile Ile Phe

755 760 765
Ile Val Leu Gln Lys Val Glu Lys Thr Leu Leu Arg Gln Gln Val Glu
770 775 780

Leu Tyr Arg Leu Leu Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Ser
785 790 795 800

Val Leu Gly Arg His Ile Phe Trp Arg Arg Leu Arg Lys Ala Leu Leu
805 810 815

Asp Gly Lys Ser Trp Asn Pro Glu Gly Thr Val Gly Thr Gly Cys Asn
820 825 830

Trp Gln Glu Ala Thr Ser Ile
835

<210> 17
<211> 782
<212> PRT
<213> Homo sapiens

<400> 17

Met Lys Pro Arg Ala Phe Arg Leu Arg Ser Leu Ser Pro Ser Pro Arg
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Phe His Cys Phe Leu Leu Asn Ala Ala Val Leu Ser Arg Arg Cys Glu
20 25 30

Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu Ser
35 40 45

Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly Ala
50 55 60

Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr Asn
65 70 75 80

Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu Lys
85 90 95

Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro Glu
100 105 110

Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser Asn
115 120 125

Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln Met
130 135 140

Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn Phe
145 150 155 160

Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr Leu
165 170 175

Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln Gly
180 185 190

Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg Asn
195 200 205

Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu Cys
210 215 220

Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr Leu
225 230 235 240

Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser Phe
245 250 255

Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr Asn
260 265 270

Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln Phe
275 280 285

Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser Asn
290 295 300

Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu Phe
305 310 315 320

Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser Gln
325 330 335

Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe Asn
340 345 350

Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu Glu
355 360 365

His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe Ser
370 375 380

Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His Thr
385 390 395 400

His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser Leu
405 410 415

Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu Pro
420 425 430

Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser Gln
435 440 445

Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser Ser
450 455 460

Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp Thr
465 470 475 480

Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser Leu
485 490 495

Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro Ser
500 505 510

Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr Cys
515 520 525

Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu Leu

530 535 540
Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln Gly
545 550 555 560

Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr Ile
565 570 575

Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala Val
580 585 590

Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys Ile
595 600 605

Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr Ser
610 615 620

Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu Glu
625 630 635 640

Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe Ile
645 650 655

Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His Lys
660 665 670

Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser Arg
675 680 685

Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu Ser
690 695 700

Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys Thr
705 710 715 720

Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn Thr
725 730 735

Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp Arg
740 745 750

Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu Gly
755 760 765

Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile
770 775 780

<210> 18
<211> 799
<212> PRT
<213> Homo sapiens

<400> 18

Met Glu Leu Asn Phe Tyr Lys Ile Pro Asp Asn Leu Pro Phe Ser Thr
1 5 10 15

Lys Asn Leu Asp Leu Ser Phe Asn Pro Leu Arg His Leu Gly Ser Tyr
20 25 30

Ser Phe Phe Ser Phe Pro Glu Leu Gln Val Leu Asp Leu Ser Arg Cys
35 40 45

Glu Ile Gln Thr Ile Glu Asp Gly Ala Tyr Gln Ser Leu Ser His Leu
50 55 60

Ser Thr Leu Ile Leu Thr Gly Asn Pro Ile Gln Ser Leu Ala Leu Gly
65 70 75 80

Ala Phe Ser Gly Leu Ser Ser Leu Gln Lys Leu Val Ala Val Glu Thr
85 90 95

Asn Leu Ala Ser Leu Glu Asn Phe Pro Ile Gly His Leu Lys Thr Leu
100 105 110

Lys Glu Leu Asn Val Ala His Asn Leu Ile Gln Ser Phe Lys Leu Pro
115 120 125

Glu Tyr Phe Ser Asn Leu Thr Asn Leu Glu His Leu Asp Leu Ser Ser
130 135 140

Asn Lys Ile Gln Ser Ile Tyr Cys Thr Asp Leu Arg Val Leu His Gln
145 150 155 160

Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn
165 170 175

Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr
180 185 190

Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln
195 200 205

Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg
210 215 220

Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu
225 230 235 240

Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr
245 250 255

Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser
260 265 270

Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr
275 280 285

Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln
290 295 300

Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser
305 310 315 320

Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu
325 330 335

Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser
340 345 350

Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe
355 360 365

Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu

370 375 380
Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe
385 390 395 400

Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His
405 410 415

Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser
420 425 430

Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu
435 440 445

Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser
450 455 460

Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser
465 470 475 480

Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp
485 490 495

Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser
500 505 510

Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro
515 520 525

Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr
530 535 540

Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu
545 550 555 560

Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln
565 570 575

Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr
580 585 590

Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala
595 600 605

Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys
610 615 620

Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr
625 630 635 640

Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu
645 650 655

Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe
660 665 670

Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His
675 680 685

Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser
690 695 700

Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu

705 710 715 720
Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys
725 730 735

Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn
740 745 750

Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp
755 760 765

Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu
770 775 780

Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile
785 790 795

<210> 19
<211> 639
<212> PRT
<213> Homo sapiens

<400> 19

Met Pro Leu Leu Asn Leu Ser Leu Asp Leu Ser Leu Asn Pro Met Asn
1 5 10 15

Phe Ile Gln Pro Gly Ala Phe Lys Glu Ile Arg Leu His Lys Leu Thr
20 25 30

Leu Arg Asn Asn Phe Asp Ser Leu Asn Val Met Lys Thr Cys Ile Gln
35 40 45

Gly Leu Ala Gly Leu Glu Val His Arg Leu Val Leu Gly Glu Phe Arg
50 55 60

Asn Glu Gly Asn Leu Glu Lys Phe Asp Lys Ser Ala Leu Glu Gly Leu
65 70 75 80

Cys Asn Leu Thr Ile Glu Glu Phe Arg Leu Ala Tyr Leu Asp Tyr Tyr
85 90 95

Leu Asp Asp Ile Ile Asp Leu Phe Asn Cys Leu Thr Asn Val Ser Ser
100 105 110

Phe Ser Leu Val Ser Val Thr Ile Glu Arg Val Lys Asp Phe Ser Tyr
115 120 125

Asn Phe Gly Trp Gln His Leu Glu Leu Val Asn Cys Lys Phe Gly Gln
130 135 140

Phe Pro Thr Leu Lys Leu Lys Ser Leu Lys Arg Leu Thr Phe Thr Ser
145 150 155 160

Asn Lys Gly Gly Asn Ala Phe Ser Glu Val Asp Leu Pro Ser Leu Glu
165 170 175

Phe Leu Asp Leu Ser Arg Asn Gly Leu Ser Phe Lys Gly Cys Cys Ser
180 185 190

Gln Ser Asp Phe Gly Thr Thr Ser Leu Lys Tyr Leu Asp Leu Ser Phe
195 200 205

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Asn Gly Val Ile Thr Met Ser Ser Asn Phe Leu Gly Leu Glu Gln Leu
    210                 215                 220

Glu His Leu Asp Phe Gln His Ser Asn Leu Lys Gln Met Ser Glu Phe
225                 230                 235                 240

Ser Val Phe Leu Ser Leu Arg Asn Leu Ile Tyr Leu Asp Ile Ser His
                245                 250                 255

Thr His Thr Arg Val Ala Phe Asn Gly Ile Phe Asn Gly Leu Ser Ser
            260                 265                 270

Leu Glu Val Leu Lys Met Ala Gly Asn Ser Phe Gln Glu Asn Phe Leu
        275                 280                 285

Pro Asp Ile Phe Thr Glu Leu Arg Asn Leu Thr Phe Leu Asp Leu Ser
    290                 295                 300

Gln Cys Gln Leu Glu Gln Leu Ser Pro Thr Ala Phe Asn Ser Leu Ser
305                 310                 315                 320

Ser Leu Gln Val Leu Asn Met Ser His Asn Asn Phe Phe Ser Leu Asp
                325                 330                 335

Thr Phe Pro Tyr Lys Cys Leu Asn Ser Leu Gln Val Leu Asp Tyr Ser
            340                 345                 350

Leu Asn His Ile Met Thr Ser Lys Lys Gln Glu Leu Gln His Phe Pro
        355                 360                 365

Ser Ser Leu Ala Phe Leu Asn Leu Thr Gln Asn Asp Phe Ala Cys Thr
    370                 375                 380

Cys Glu His Gln Ser Phe Leu Gln Trp Ile Lys Asp Gln Arg Gln Leu
385                 390                 395                 400

Leu Val Glu Val Glu Arg Met Glu Cys Ala Thr Pro Ser Asp Lys Gln
                405                 410                 415

Gly Met Pro Val Leu Ser Leu Asn Ile Thr Cys Gln Met Asn Lys Thr
            420                 425                 430

Ile Ile Gly Val Ser Val Leu Ser Val Leu Val Val Ser Val Val Ala
        435                 440                 445

Val Leu Val Tyr Lys Phe Tyr Phe His Leu Met Leu Leu Ala Gly Cys
    450                 455                 460

Ile Lys Tyr Gly Arg Gly Glu Asn Ile Tyr Asp Ala Phe Val Ile Tyr
465                 470                 475                 480

Ser Ser Gln Asp Glu Asp Trp Val Arg Asn Glu Leu Val Lys Asn Leu
                485                 490                 495

Glu Glu Gly Val Pro Pro Phe Gln Leu Cys Leu His Tyr Arg Asp Phe
            500                 505                 510

Ile Pro Gly Val Ala Ile Ala Ala Asn Ile Ile His Glu Gly Phe His
        515                 520                 525

Lys Ser Arg Lys Val Ile Val Val Val Ser Gln His Phe Ile Gln Ser
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530 535 540
Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala Gln Thr Trp Gln Phe Leu
545 550 555 560

Ser Ser Arg Ala Gly Ile Ile Phe Ile Val Leu Gln Lys Val Glu Lys
565 570 575

Thr Leu Leu Arg Gln Gln Val Glu Leu Tyr Arg Leu Leu Ser Arg Asn
580 585 590

Thr Tyr Leu Glu Trp Glu Asp Ser Val Leu Gly Arg His Ile Phe Trp
595 600 605

Arg Arg Leu Arg Lys Ala Leu Leu Asp Gly Lys Ser Trp Asn Pro Glu
610 615 620

Gly Thr Val Gly Thr Gly Cys Asn Trp Gln Glu Ala Thr Ser Ile
625 630 635

<210> 20
<211> 3866
<212> DNA
<213> murine

<400> 20
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gcactgttct tctcctgcct gacaccagga agcttgaatc cctgcataga ggtagttcct 120

aatattacct accaatgcat ggatcagaaa ctcagcaaag tccctgatga cattccttct 180

tcaaccaaga acatagatct gagcttcaac cccttgaaga tcttaaaaag ctatagcttc 240

tccaattttt cagaacttca gtggctggat ttatccaggt gtgaaattga aacaattgaa 300

gacaaggcat ggcatggctt acaccacctc tcaaacttga tactgacagg aaaccctatc 360

cagagttttt ccccaggaag tttctctgga ctaacaagtt tagagaatct ggtggctgtg 420

gagacaaaat tggcctctct agaaagcttc cctattggac agcttataac cttaaagaaa 480

ctcaatgtgg ctcacaattt tatacattcc tgtaagttac ctgcatattt ttccaatctg 540

acgaacctag tacatgtgga tctttcttat aactatattc aaactattac tgtcaacgac 600

ttacagtttc tacgtgaaaa tccacaagtc aatctctctt tagacatgtc tttgaaccca 660

attgacttca ttcaagacca agcctttcag ggaattaagc tccatgaact gactctaaga 720

ggtaatttta atagctcaaa tataatgaaa acttgccttc aaaacctggc tggtttacac 780

gtccatcggt tgatcttggg agaatttaaa gatgaaagga atctggaaat tttgaaccc 840

tctatcatgg aaggactatg tgatgtgacc attgatgagt tcaggttaac atatacaaat 900

gatttttcag atgatattgt taagttccat tgcttggcga atgtttctgc aatgtctctg 960

gcaggtgtat ctataaaata tctagaagat gttcctaaac atttcaaatg gcaatcctta 1020

tcaatcatta gatgtcaact taagcagttt ccaactctgg atctaccctt tcttaaaagt 1080

ttgactttaa ctatgaacaa agggtctatc agttttaaaa aagtggccct accaagtctc 1140
agctatctag atcttagtag aaatgcactg agctttagtg gttgctgttc ttattctgat 1200

ttgggaacaa acagcctgag acacttagac ctcagcttca atggtgccat cattatgagt 1260

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Pro Val Glu Met Asn Thr Ser Leu Val Leu Asp Phe Asn Asn Ser Thr
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Cys Tyr Met Tyr Lys Thr Ile Ile Ser Val Ser Val Val Ser Val Ile
625                 630                 635                 640

Val Val Ser Thr Val Ala Phe Leu Ile Tyr His Phe Tyr Phe His Leu
                645                 650                 655

Ile Leu Ile Ala Gly Cys Lys Lys Tyr Ser Arg Gly Glu Ser Ile Tyr
            660                 665                 670

Asp Ala Phe Val Ile Tyr Ser Ser Gln Asn Glu Asp Trp Val Arg Asn
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            675                 680                 685
Glu Leu Val Lys Asn Leu Glu Glu Gly Val Pro Arg Phe His Leu Cys
    690                 695                 700

Leu His Tyr Arg Asp Phe Ile Pro Gly Val Ala Ile Ala Ala Asn Ile
705                 710                 715                 720

Ile Gln Glu Gly Phe His Lys Ser Arg Lys Val Ile Val Val Val Ser
                725                 730                 735

Arg His Phe Ile Gln Ser Arg Trp Cys Ile Phe Glu Tyr Glu Ile Ala
            740                 745                 750

Gln Thr Trp Gln Phe Leu Ser Ser His Ser Gly Ile Ile Phe Ile Val
        755                 760                 765

Leu Glu Lys Val Glu Lys Ser Leu Leu Arg Gln Gln Val Glu Leu Tyr
    770                 775                 780

Arg Leu Leu Ser Arg Asn Thr Tyr Leu Glu Trp Glu Asp Asn Pro Leu
785                 790                 795                 800

Gly Arg His Ile Phe Trp Arg Arg Leu Lys Asn Ala Leu Leu Asp Gly
                805                 810                 815

Lys Ala Ser Asn Pro Glu Gln Thr Ala Glu Glu Glu Gln Glu Thr Ala
            820                 825                 830

Thr Trp Thr
        835
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<210> 25
<211> 3431
<212> DNA
<213> Homo sapiens

<400> 25

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cgcaggcggc gcggggaggc gtcccagagt ctcactctgc cgcccaggct ggactgcagt     180

gacacaatct cggctgactg caaccactgc ctccagggtt caagcgattc tcttgcctca     240

gcctccccaag tagctgggat tacagattga tgttcatgtt cctggcacta ctacaagatt    300

catactcctg atgctactga caacgtggct tctccacagt caccaaacca gggatgctat     360

actggacttc cctactctca tctgctccag ccccctgacc ttatagttgc ccagctttcc     420

tggcaattga ctttgcccat caatacacag gatttagcat ccagggaaga tgtcggagcc     480

tcagatgtta attttctaat tgagaatgtt ggcgctgtcc gaacctggag acagaaaaac     540

aaaaagtcct ttctcctgat tcaccaaaaa ataaaatact gactaccatc actgtgatga     600

gattcctata gtctcaggaa ctgaagtctt taaacaacca gggaccctct gcccctagaa     660

taagaacata ctagaagtcc cttctgctag gacaacgagg atcatgggag accacctgga     720
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ttatctcaag ccacaaataa ctcttcactt tgtatttgca ccaagttatc attttggggt 3360

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ttcgtatcaa a 3431

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<211> 858
<212> PRT
<213> Homo sapiens

<400> 26

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Tyr Arg Phe Cys Asn Leu Thr Gln Val Pro Gln Val Leu Asn Thr Thr
35 40 45

Glu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser
50 55 60

Ser Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln
65 70 75 80

Tyr Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn
85 90 95

Leu Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro
100 105 110

Asp Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu Tyr Phe
115 120 125

Cys Gly Leu Ser Asp Ala Val Leu Lys Asp Gly Tyr Phe Arg Asn Leu

130 135 140
Lys Ala Leu Thr Arg Leu Asp Leu Ser Lys Asn Gln Ile Arg Ser Leu
145 150 155 160

Tyr Leu His Pro Ser Phe Gly Lys Leu Asn Ser Leu Lys Ser Ile Asp
165 170 175

Phe Ser Ser Asn Gln Ile Phe Leu Val Cys Glu His Glu Leu Glu Pro
180 185 190

Leu Gln Gly Lys Thr Leu Ser Phe Phe Ser Leu Ala Ala Asn Ser Leu
195 200 205

Tyr Ser Arg Val Ser Val Asp Trp Gly Lys Cys Met Asn Pro Phe Arg
210 215 220

Asn Met Val Leu Glu Ile Leu Asp Val Ser Gly Asn Gly Trp Thr Val
225 230 235 240

Asp Ile Thr Gly Asn Phe Ser Asn Ala Ile Ser Lys Ser Gln Ala Phe
245 250 255

Ser Leu Ile Leu Ala His His Ile Met Gly Ala Gly Phe Gly Phe His
260 265 270

Asn Ile Lys Asp Pro Asp Gln Asn Thr Phe Ala Gly Leu Ala Arg Ser
275 280 285

Ser Val Arg His Leu Asp Leu Ser His Gly Phe Val Phe Ser Leu Asn
290 295 300

Ser Arg Val Phe Glu Thr Leu Lys Asp Leu Lys Val Leu Asn Leu Ala
305 310 315 320

Tyr Asn Lys Ile Asn Lys Ile Ala Asp Glu Ala Phe Tyr Gly Leu Asp
325 330 335

Asn Leu Gln Val Leu Asn Leu Ser Tyr Asn Leu Leu Gly Glu Leu Tyr
340 345 350

Ser Ser Asn Phe Tyr Gly Leu Pro Lys Val Ala Tyr Ile Asp Leu Gln
355 360 365

Lys Asn His Ile Ala Ile Ile Gln Asp Gln Thr Phe Lys Phe Leu Glu
370 375 380

Lys Leu Gln Thr Leu Asp Leu Arg Asp Asn Ala Leu Thr Thr Ile His
385 390 395 400

Phe Ile Pro Ser Ile Pro Asp Ile Phe Leu Ser Gly Asn Lys Leu Val
405 410 415

Thr Leu Pro Lys Ile Asn Leu Thr Ala Asn Leu Ile His Leu Ser Glu
420 425 430

Asn Arg Leu Glu Asn Leu Asp Ile Leu Tyr Phe Leu Leu Arg Val Pro
435 440 445

His Leu Gln Ile Leu Ile Leu Asn Gln Asn Arg Phe Ser Ser Cys Ser
450 455 460

Gly Asp Gln Thr Pro Ser Glu Asn Pro Ser Leu Glu Gln Leu Phe Leu

465 470 475 480
Gly Glu Asn Met Leu Gln Leu Ala Trp Glu Thr Glu Leu Cys Trp Asp
485 490 495

Val Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu Asn His Asn
500 505 510

Tyr Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu Thr Ala Leu
515 520 525

Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu Ser His Asn
530 535 540

Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg Asn Gln Leu
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Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val Leu Asp Ile
565 570 575

Thr His Asn Lys Phe Ile Cys Glu Cys Glu Leu Ser Thr Phe Ile Asn
580 585 590

Trp Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro Ala Asp Ile
595 600 605

Tyr Cys Val Tyr Pro Asp Ser Phe Ser Gly Val Ser Leu Phe Ser Leu
610 615 620

Ser Thr Glu Gly Cys Asp Glu Glu Glu Val Leu Lys Ser Leu Lys Phe
625 630 635 640

Ser Leu Phe Ile Val Cys Thr Val Thr Leu Thr Leu Phe Leu Met Thr
645 650 655

Ile Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile Cys Tyr Lys
660 665 670

Thr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly Thr Glu Pro
675 680 685

Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser Lys Asp Phe
690 695 700

Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln Tyr Ser
705 710 715 720

Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe Val Pro
725 730 735

Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn Ser Arg
740 745 750

Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly Trp Cys
755 760 765

Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp Leu Asn
770 775 780

Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr Gln Leu
785 790 795 800

Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln Tyr Leu

805 810 815
Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His Lys Leu
820 825 830

Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp Asn Asn
835 840 845

Ile Pro Leu Gln Thr Val Ala Thr Ile Ser
850 855

<210> 27
<211> 858
<212> PRT
<213> Homo sapiens

<400> 27

Met Gly Asp His Leu Asp Leu Leu Leu Gly Val Val Leu Met Ala Gly
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Pro Val Phe Gly Ile Pro Ser Cys Ser Phe Asp Gly Arg Ile Ala Phe
20 25 30

Tyr Arg Phe Cys Asn Leu Thr Gln Val Pro Gln Val Leu Asn Thr Thr
35 40 45

Glu Arg Leu Leu Leu Ser Phe Asn Tyr Ile Arg Thr Val Thr Ala Ser
50 55 60

Ser Phe Pro Phe Leu Glu Gln Leu Gln Leu Leu Glu Leu Gly Ser Gln
65 70 75 80

Tyr Thr Pro Leu Thr Ile Asp Lys Glu Ala Phe Arg Asn Leu Pro Asn
85 90 95

Leu Arg Ile Leu Asp Leu Gly Ser Ser Lys Ile Tyr Phe Leu His Pro
100 105 110

Asp Ala Phe Gln Gly Leu Phe His Leu Phe Glu Leu Arg Leu Tyr Phe
115 120 125

Cys Gly Leu Ser Asp Ala Val Leu Lys Asp Gly Tyr Phe Arg Asn Leu
130 135 140

Lys Ala Leu Thr Arg Leu Asp Leu Ser Lys Asn Gln Ile Arg Ser Leu
145 150 155 160

Tyr Leu His Pro Ser Phe Gly Lys Leu Asn Ser Leu Lys Ser Ile Asp
165 170 175

Phe Ser Ser Asn Gln Ile Phe Leu Val Cys Glu His Glu Leu Glu Pro
180 185 190

Leu Gln Gly Lys Thr Leu Ser Phe Phe Ser Leu Ala Ala Asn Ser Leu
195 200 205

Tyr Ser Arg Val Ser Val Asp Trp Gly Lys Cys Met Asn Pro Phe Arg
210 215 220

Asn Met Val Leu Glu Ile Val Asp Val Ser Gly Asn Gly Trp Thr Val
225 230 235 240

Asp Ile Thr Gly Asn Phe Ser Asn Ala Ile Ser Lys Ser Gln Ala Phe
245 250 255

Ser Leu Ile Leu Ala His His Ile Met Gly Ala Gly Phe Gly Phe His
260 265 270

Asn Ile Lys Asp Pro Asp Gln Asn Thr Phe Ala Gly Leu Ala Arg Ser
275 280 285

Ser Val Arg His Leu Asp Leu Ser His Gly Phe Val Phe Ser Leu Asn
290 295 300

Ser Arg Val Phe Glu Thr Leu Lys Asp Leu Lys Val Leu Asn Leu Ala
305 310 315 320

Tyr Asn Lys Ile Asn Lys Ile Ala Asp Glu Ala Phe Tyr Gly Leu Asp
325 330 335

Asn Leu Gln Val Leu Asn Leu Ser Tyr Asn Leu Leu Gly Glu Leu Cys
340 345 350

Ser Ser Asn Phe Tyr Gly Leu Pro Lys Val Ala Tyr Ile Asp Leu Gln
355 360 365

Lys Asn His Ile Ala Ile Ile Gln Asp Gln Thr Phe Lys Phe Leu Glu
370 375 380

Lys Leu Gln Thr Leu Asp Leu Arg Asp Asn Ala Leu Thr Thr Ile His
385 390 395 400

Phe Ile Pro Ser Ile Pro Asp Ile Phe Leu Ser Gly Asn Lys Leu Val
405 410 415

Thr Leu Pro Lys Ile Asn Leu Thr Ala Asn Leu Ile His Leu Ser Glu
420 425 430

Asn Arg Leu Glu Asn Leu Asp Ile Leu Tyr Phe Leu Leu Arg Val Pro
435 440 445

His Leu Gln Ile Leu Ile Leu Asn Gln Asn Arg Phe Ser Ser Cys Ser
450 455 460

Gly Asp Gln Thr Pro Ser Glu Asn Pro Ser Leu Glu Gln Leu Phe Leu
465 470 475 480

Gly Glu Asn Met Leu Gln Leu Ala Trp Glu Thr Glu Leu Cys Trp Asp
485 490 495

Val Phe Glu Gly Leu Ser His Leu Gln Val Leu Tyr Leu Asn His Asn
500 505 510

Tyr Leu Asn Ser Leu Pro Pro Gly Val Phe Ser His Leu Thr Ala Leu
515 520 525

Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu Ser His Asn
530 535 540

Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg Asn Gln Leu
545 550 555 560

Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val Leu Asp Ile

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                565                 570                 575
Thr His Asn Lys Phe Ile Cys Glu Cys Glu Leu Ser Thr Phe Ile Asn
            580                 585                 590

Trp Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro Ala Asp Ile
        595                 600                 605

Tyr Cys Val Tyr Pro Asp Ser Phe Ser Gly Val Ser Leu Phe Ser Leu
    610                 615                 620

Ser Thr Glu Gly Cys Asp Glu Glu Glu Val Leu Lys Ser Leu Lys Phe
625                 630                 635                 640

Ser Leu Phe Ile Val Cys Thr Val Thr Leu Thr Leu Phe Leu Met Thr
                645                 650                 655

Ile Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile Cys Tyr Lys
            660                 665                 670

Thr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly Thr Glu Pro
        675                 680                 685

Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser Lys Asp Phe
    690                 695                 700

Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr Gln Tyr Ser
705                 710                 715                 720

Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp Phe Val Pro
                725                 730                 735

Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp Asn Ser Arg
            740                 745                 750

Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp Gly Trp Cys
        755                 760                 765

Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser Asp Leu Asn
    770                 775                 780

Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln Tyr Gln Leu
785                 790                 795                 800

Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln Gln Tyr Leu
                805                 810                 815

Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu His Lys Leu
            820                 825                 830

Ser Gln Gln Ile Leu Lys Lys Glu Lys Glu Lys Lys Lys Asp Asn Asn
        835                 840                 845

Ile Pro Leu Gln Thr Val Ala Thr Ile Ser
    850                 855
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<210> 28
<211> 365
<212> PRT
<213> Homo sapiens

<400> 28

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            20                  25                  30

Thr Ala Leu Arg Gly Leu Ser Leu Asn Ser Asn Arg Leu Thr Val Leu
        35                  40                  45

Ser His Asn Asp Leu Pro Ala Asn Leu Glu Ile Leu Asp Ile Ser Arg
    50                  55                  60

Asn Gln Leu Leu Ala Pro Asn Pro Asp Val Phe Val Ser Leu Ser Val
65                  70                  75                  80

Leu Asp Ile Thr His Asn Lys Phe Ile Cys Glu Cys Glu Leu Ser Thr
                85                  90                  95

Phe Ile Asn Trp Leu Asn His Thr Asn Val Thr Ile Ala Gly Pro Pro
            100                 105                 110

Ala Asp Ile Tyr Cys Val Tyr Pro Asp Ser Phe Ser Gly Val Ser Leu
        115                 120                 125

Phe Ser Leu Ser Thr Glu Gly Cys Asp Glu Glu Glu Val Leu Lys Ser
    130                 135                 140

Leu Lys Phe Ser Leu Phe Ile Val Cys Thr Val Thr Leu Thr Leu Phe
145                 150                 155                 160

Leu Met Thr Ile Leu Thr Val Thr Lys Phe Arg Gly Phe Cys Phe Ile
                165                 170                 175

Cys Tyr Lys Thr Ala Gln Arg Leu Val Phe Lys Asp His Pro Gln Gly
            180                 185                 190

Thr Glu Pro Asp Met Tyr Lys Tyr Asp Ala Tyr Leu Cys Phe Ser Ser
        195                 200                 205

Lys Asp Phe Thr Trp Val Gln Asn Ala Leu Leu Lys His Leu Asp Thr
    210                 215                 220

Gln Tyr Ser Asp Gln Asn Arg Phe Asn Leu Cys Phe Glu Glu Arg Asp
225                 230                 235                 240

Phe Val Pro Gly Glu Asn Arg Ile Ala Asn Ile Gln Asp Ala Ile Trp
                245                 250                 255

Asn Ser Arg Lys Ile Val Cys Leu Val Ser Arg His Phe Leu Arg Asp
            260                 265                 270

Gly Trp Cys Leu Glu Ala Phe Ser Tyr Ala Gln Gly Arg Cys Leu Ser
        275                 280                 285

Asp Leu Asn Ser Ala Leu Ile Met Val Val Val Gly Ser Leu Ser Gln
    290                 295                 300

Tyr Gln Leu Met Lys His Gln Ser Ile Arg Gly Phe Val Gln Lys Gln
305                 310                 315                 320

Gln Tyr Leu Arg Trp Pro Glu Asp Leu Gln Asp Val Gly Trp Phe Leu
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325 330 335
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Asp Asn Asn Ile Pro Leu Gln Thr Val Ala Thr Ile Ser
355 360 365

<210> 29
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<400> 29
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aatagccatt attttcaatc agaaggaatt actcatatgc taaactttac caagaaccta 1920
aaggttctgc agaaactgat gatgaacgac aatgacatct cttcctccac cagcaggacc 1980
atggagagtg agtctcttag aactctggaa ttcagaggaa atcacttaga tgttttatgg 2040
agagaaggtg ataacagata cttacaatta ttcaagaatc tgctaaaatt agaggaatta 2100
gacatctcta aaaattccct aagtttcttg ccttctggag tttttgatgg tatgcctcca 2160
aatctaaaga atctctcttt ggccaaaaat gggctcaaat ctttcagttg gaagaaactc 2220
cagtgtctaa agaacctgga aactttggac ctcagccaca accaactgac cactgtccct 2280
gagagattat ccaactgttc cagaagcctc aagaatctga ttcttaagaa taatcaaatc 2340
aggagtctga cgaagtattt tctacaagat gccttccagt tgcgatatct ggatctcagc 2400
tcaaataaaa tccagatgat ccaaaagacc agcttcccag aaaatgtcct caacaatctg 2460
aagatgttgc ttttgcatca taatcggttt ctgtgcacct gtgatgctgt gtggtttgtc 2520
tggtgggtta accatacgga ggtgactatt ccttacctgg ccacagatgt gacttgtgtg 2580
gggccaggag cacacaaggg ccaaagtgtg atctccctgg atctgtacac ctgtgagtta 2640
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atgatgacag caagtcacct ctatttctgg gatgtgtggt atatttacca tttctgtaag 2760
gccaagataa aggggtatca gcgtctaata tcaccagact gttgctatga tgcttttatt 2820
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gtgatgacag acaagtatgc aaagactgaa aattttaaga tagcatttta cttgtcccat 3060
cagaggctca tggatgaaaa agttgatgtg attatcttga tatttcttga gaagcccttt 3120
cagaagtcca agttcctcca gctccggaaa aggctctgtg ggagttctgt ccttgagtgg 3180
ccaacaaacc cgcaagctca cccatacttc tggcagtgtc taaagaacgc cctggccaca 3240
gacaatcatg tggcctatag tcaggtgttc aaggaaacgg tctagccctt ctttgcaaaa 3300

cacaactgcc tagtttacca aggagaggcc tggctgttta aattgttttc atatatatca 3360

caccaaaagc gtgttttgaa attcttcaag aaatgagatt gcccatattt caggggag 3418

<210> 34
<211> 1049
<212> PRT
<213> Homo sapiens

<400> 34

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe
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Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
65 70 75 80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
85 90 95

Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
100 105 110

Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
115 120 125

Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
210 215 220

Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
225 230 235 240

Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro

260 265 270
Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
290 295 300

Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
305 310 315 320

Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
340 345 350

Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
355 360 365

Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
370 375 380

Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met
405 410 415

Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
420 425 430

Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
435 440 445

Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His
450 455 460

Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
465 470 475 480

Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln
485 490 495

Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp
500 505 510

Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu
515 520 525

Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu
530 535 540

Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr
545 550 555 560

Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn
565 570 575

Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr
580 585 590

Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile

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        595                 600                 605
Ser Ser Ser Thr Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu
    610                 615                 620

Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn
625                 630                 635                 640

Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp
                645                 650                 655

Ile Ser Lys Asn Ser Leu Ser Phe Leu Pro Ser Gly Val Phe Asp Gly
            660                 665                 670

Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys
        675                 680                 685

Ser Phe Ser Trp Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu
    690                 695                 700

Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn
705                 710                 715                 720

Cys Ser Arg Ser Leu Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg
                725                 730                 735

Ser Leu Thr Lys Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu
            740                 745                 750

Asp Leu Ser Ser Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro
        755                 760                 765

Glu Asn Val Leu Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg
    770                 775                 780

Phe Leu Cys Thr Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His
785                 790                 795                 800

Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly
                805                 810                 815

Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr
            820                 825                 830

Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser
        835                 840                 845

Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe
    850                 855                 860

Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly
865                 870                 875                 880

Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val
                885                 890                 895

Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu
            900                 905                 910

Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu
        915                 920                 925

Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser
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930 935 940
Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys
945 950 955 960

Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln
965 970 975

Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu
980 985 990

Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys
995 1000 1005

Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro
1010 1015 1020

Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Ala Thr Asp Asn His
1025 1030 1035

Val Ala Tyr Ser Gln Val Phe Lys Glu Thr Val
1040 1045

<210> 35
<211> 1049
<212> PRT
<213> Homo sapiens

<400> 35

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe
1 5 10 15

Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
65 70 75 80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
85 90 95

Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
100 105 110

Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
115 120 125

Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
210 215 220

Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
225 230 235 240

Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
260 265 270

Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
290 295 300

Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
305 310 315 320

Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
340 345 350

Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
355 360 365

Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
370 375 380

Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met
405 410 415

Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
420 425 430

Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
435 440 445

Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His
450 455 460

Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
465 470 475 480

Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln
485 490 495

Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp

500 505 510
Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu
515 520 525

Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu
530 535 540

Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr
545 550 555 560

Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn
565 570 575

Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr
580 585 590

Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile
595 600 605

Ser Ser Ser Thr Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu
610 615 620

Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn
625 630 635 640

Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp
645 650 655

Ile Ser Lys Asn Ser Leu Ser Phe Leu Pro Ser Gly Val Phe Asp Gly
660 665 670

Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys
675 680 685

Ser Phe Ser Trp Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu
690 695 700

Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn
705 710 715 720

Cys Ser Arg Ser His Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg
725 730 735

Ser Pro Thr Lys Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu
740 745 750

Asp Leu Ser Ser Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro
755 760 765

Glu Asn Val Leu Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg
770 775 780

Phe Leu Cys Thr Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His
785 790 795 800

Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly
805 810 815

Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr
820 825 830

Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser

835 840 845
Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe
850 855 860

Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly
865 870 875 880

Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val
885 890 895

Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu
900 905 910

Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu
915 920 925

Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser
930 935 940

Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys
945 950 955 960

Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln
965 970 975

Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu
980 985 990

Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys
995 1000 1005

Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro
1010 1015 1020

Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Ala Thr Asp Asn His
1025 1030 1035

Val Ala Tyr Ser Gln Val Phe Lys Glu Thr Val
1040 1045

<210> 36
<211> 1049
<212> PRT
<213> Homo spaiens

<400> 36

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe
1 5 10 15

Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
65 70 75 80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
85 90 95

Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
100 105 110

Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
115 120 125

Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
210 215 220

Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
225 230 235 240

Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
260 265 270

Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
290 295 300

Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
305 310 315 320

Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
340 345 350

Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
355 360 365

Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
370 375 380

Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met

405 410 415
Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
420 425 430

Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
435 440 445

Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His
450 455 460

Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
465 470 475 480

Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln
485 490 495

Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp
500 505 510

Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu
515 520 525

Ile Ser Gln Thr Leu Asn Gly Ser Glu Phe Gln Pro Leu Ala Glu Leu
530 535 540

Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu His Ser Thr
545 550 555 560

Ala Phe Glu Glu Leu His Lys Leu Glu Val Leu Asp Ile Ser Ser Asn
565 570 575

Ser His Tyr Phe Gln Ser Glu Gly Ile Thr His Met Leu Asn Phe Thr
580 585 590

Lys Asn Leu Lys Val Leu Gln Lys Leu Met Met Asn Asp Asn Asp Ile
595 600 605

Ser Ser Ser Thr Ser Arg Thr Met Glu Ser Glu Ser Leu Arg Thr Leu
610 615 620

Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Glu Gly Asp Asn
625 630 635 640

Arg Tyr Leu Gln Leu Phe Lys Asn Leu Leu Lys Leu Glu Glu Leu Asp
645 650 655

Ile Ser Lys Asn Ser Leu Ser Phe Leu Pro Ser Gly Val Phe Asp Gly
660 665 670

Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu Lys
675 680 685

Ser Phe Ser Trp Lys Lys Leu Gln Cys Leu Lys Asn Leu Glu Thr Leu
690 695 700

Asp Leu Ser His Asn Gln Leu Thr Thr Val Pro Glu Arg Leu Ser Asn
705 710 715 720

Cys Ser Arg Ser Leu Lys Asn Leu Ile Leu Lys Asn Asn Gln Ile Arg
725 730 735

Ser Leu Thr Lys Tyr Phe Leu Gln Asp Ala Phe Gln Leu Arg Tyr Leu

740 745 750
Asp Leu Ser Ser Asn Lys Ile Gln Met Ile Gln Lys Thr Ser Phe Pro
755 760 765

Glu Asn Val Leu Asn Asn Leu Lys Met Leu Leu Leu His His Asn Arg
770 775 780

Phe Leu Cys Thr Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn His
785 790 795 800

Thr Glu Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val Gly
805 810 815

Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr Thr
820 825 830

Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Leu Ser Ile Ser
835 840 845

Val Ser Leu Phe Leu Met Val Met Met Thr Ala Ser His Leu Tyr Phe
850 855 860

Trp Asp Val Trp Tyr Ile Tyr His Phe Cys Lys Ala Lys Ile Lys Gly
865 870 875 880

Tyr Gln Arg Leu Ile Ser Pro Asp Cys Cys Tyr Asp Ala Phe Ile Val
885 890 895

Tyr Asp Thr Lys Asp Pro Ala Val Thr Glu Trp Val Leu Ala Glu Leu
900 905 910

Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys Leu
915 920 925

Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu Ser
930 935 940

Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Asp Lys
945 950 955 960

Tyr Ala Lys Thr Glu Asn Phe Lys Ile Ala Phe Tyr Leu Ser His Gln
965 970 975

Arg Leu Met Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu Glu
980 985 990

Lys Pro Phe Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu Cys
995 1000 1005

Gly Ser Ser Val Leu Glu Trp Pro Thr Asn Pro Gln Ala His Pro
1010 1015 1020

Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Ala Thr Asp Asn His
1025 1030 1035

Val Ala Tyr Ser Gln Val Phe Lys Glu Thr Val
1040 1045

<210> 37
<211> 1049
<212> PRT

<213> Homo sapiens
<400> 37

Met Val Phe Pro Met Trp Thr Leu Lys Arg Gln Ile Leu Ile Leu Phe
1 5 10 15

Asn Ile Ile Leu Ile Ser Lys Leu Leu Gly Ala Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Asp Val Thr Leu Asp Val Pro Lys Asn His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Gly Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Asp Ile
65 70 75 80

Ser Pro Ala Ser Phe His Arg Leu Asp His Leu Val Glu Ile Asp Phe
85 90 95

Arg Cys Asn Cys Val Pro Ile Pro Leu Gly Ser Lys Asn Asn Met Cys
100 105 110

Ile Lys Arg Leu Gln Ile Lys Pro Arg Ser Phe Ser Gly Leu Thr Tyr
115 120 125

Leu Lys Ser Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Gly Leu Pro Pro Ser Leu Gln Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Arg Lys Glu Asn Leu Thr Glu Leu Ala Asn Ile Glu Ile
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Tyr Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Asn Leu Thr Lys Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Val Leu Pro
210 215 220

Ser Thr Leu Thr Glu Leu Tyr Leu Tyr Asn Asn Met Ile Ala Lys Ile
225 230 235 240

Gln Glu Asp Asp Phe Asn Asn Leu Asn Gln Leu Gln Ile Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Ala Pro Phe Pro Cys Ala Pro
260 265 270

Cys Lys Asn Asn Ser Pro Leu Gln Ile Pro Val Asn Ala Phe Asp Ala
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
290 295 300

Val Pro Pro Arg Trp Phe Lys Asn Ile Asn Lys Leu Gln Glu Leu Asp
305 310 315 320

Leu Ser Gln Asn Phe Leu Ala Lys Glu Ile Gly Asp Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Ser Leu Ile Gln Leu Asp Leu Ser Phe Asn Phe Glu
340 345 350

Leu Gln Val Tyr Arg Ala Ser Met Asn Leu Ser Gln Ala Phe Ser Ser
355 360 365

Leu Lys Ser Leu Lys Ile Leu Arg Ile Arg Gly Tyr Val Phe Lys Glu
370 375 380

Leu Lys Ser Phe Asn Leu Ser Pro Leu His Asn Leu Gln Asn Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asn Leu Ser Met
405 410 415

Phe Lys Gln Phe Lys Arg Leu Lys Val Ile Asp Leu Ser Val Asn Lys
420 425 430

Ile Ser Pro Ser Gly Asp Ser Ser Glu Val Gly Phe Cys Ser Asn Ala
435 440 445

Arg Thr Ser Val Glu Ser Tyr Glu Pro Gln Val Leu Glu Gln Leu His
450 455 460

Tyr Phe Arg Tyr Asp Lys Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
465 470 475 480

Glu Ala Ser Phe Met Ser Val Asn Glu Ser Cys Tyr Lys Tyr Gly Gln
485 490 495

Thr Leu Asp Leu Ser Lys Asn Ser Ile Phe Phe Val Lys Ser Ser Asp
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Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn Leu
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Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His
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Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
465 470 475 480

Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly
485 490 495

Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser
500 505 510

Asp Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn
515 520 525

Thr Ile Gly Gln Thr Leu Asn Gly Ser Glu Leu Trp Pro Leu Arg Glu
530 535 540

Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser
545 550 555 560

Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser

565 570 575

Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
580 585 590

Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
595 600 605

Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile
610 615 620

Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp
625 630 635 640

Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu
645 650 655

Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu
660 665 670

Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu
675 680 685

Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile
690 695 700

Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala
705 710 715 720

Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile
725 730 735

Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr
740 745 750

Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe
755 760 765

Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn
770 775 780

Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn
785 790 795 800

His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val
805 810 815

Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr
820 825 830

Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile
835 840 845

Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe
850 855 860

Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys
865 870 875 880

Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile
885 890 895

Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu

900 905 910
Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys
915 920 925

Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu
930 935 940

Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln
945 950 955 960

Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
965 970 975

Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
980 985 990

Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
995 1000 1005

Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
1010 1015 1020

Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn
1025 1030 1035

His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
1040 1045 1050

<210> 42
<211> 1050
<212> PRT
<213> murine

<400> 42

Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
1 5 10 15

Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
65 70 75 80

Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
85 90 95

Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
100 105 110

Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
115 120 125

Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
210 215 220

Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile
225 230 235 240

Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro
260 265 270

Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
290 295 300

Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp
305 310 315 320

Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu
340 345 350

Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser
355 360 365

Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu
370 375 380

Leu Lys Asn Ser Ser Leu Ser Val Leu His Lys Leu Pro Arg Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile
405 410 415

Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys
420 425 430

Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala
435 440 445

Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His
450 455 460

Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys

465 470 475 480
Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly
485 490 495

Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser
500 505 510

Asp Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn
515 520 525

Thr Ile Gly Gln Thr Leu Asn Gly Ser Glu Leu Trp Pro Leu Arg Glu
530 535 540

Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser
545 550 555 560

Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser
565 570 575

Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
580 585 590

Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
595 600 605

Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile
610 615 620

Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp
625 630 635 640

Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu
645 650 655

Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu
660 665 670

Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu
675 680 685

Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile
690 695 700

Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala
705 710 715 720

Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile
725 730 735

Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr
740 745 750

Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe
755 760 765

Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn
770 775 780

Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn
785 790 795 800

His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val

805 810 815
Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr
820 825 830

Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile
835 840 845

Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe
850 855 860

Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys
865 870 875 880

Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile
885 890 895

Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu
900 905 910

Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys
915 920 925

Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu
930 935 940

Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln
945 950 955 960

Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
965 970 975

Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
980 985 990

Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
995 1000 1005

Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
1010 1015 1020

Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn
1025 1030 1035

His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
1040 1045 1050

<210> 43
<211> 1050
<212> PRT
<213> murine

<400> 43

Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
1 5 10 15

Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
65 70 75 80

Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
85 90 95

Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
100 105 110

Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
115 120 125

Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
210 215 220

Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile
225 230 235 240

Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro
260 265 270

Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
290 295 300

Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp
305 310 315 320

Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu
340 345 350

Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser
355 360 365

Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu

370 375 380
Leu Lys Asn Ser Ser Leu Ser Val Leu His Lys Leu Pro Arg Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile
405 410 415

Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys
420 425 430

Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala
435 440 445

Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His
450 455 460

Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
465 470 475 480

Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly
485 490 495

Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser
500 505 510

Asp Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn
515 520 525

Thr Ile Gly Gln Thr Leu Asn Gly Ser Glu Leu Trp Pro Leu Arg Glu
530 535 540

Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser
545 550 555 560

Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser
565 570 575

Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
580 585 590

Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
595 600 605

Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile
610 615 620

Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp
625 630 635 640

Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu
645 650 655

Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu
660 665 670

Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu
675 680 685

Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile
690 695 700

Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala

705 710 715 720
Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile
725 730 735

Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr
740 745 750

Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe
755 760 765

Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn
770 775 780

Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn
785 790 795 800

His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val
805 810 815

Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr
820 825 830

Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile
835 840 845

Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe
850 855 860

Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys
865 870 875 880

Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile
885 890 895

Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu
900 905 910

Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys
915 920 925

Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu
930 935 940

Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln
945 950 955 960

Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
965 970 975

Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
980 985 990

Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
995 1000 1005

Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
1010 1015 1020

Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn
1025 1030 1035

His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val

1040 1045 1050

<210> 44
<211> 1050
<212> PRT
<213> murine

<400> 44

Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
1 5 10 15

Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
65 70 75 80

Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
85 90 95

Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
100 105 110

Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
115 120 125

Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
210 215 220

Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile
225 230 235 240

Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro
260 265 270

Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
    290   295   300

Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp
305   310   315   320

Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu
                325   330   335

His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu
            340   345   350

Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser
        355   360   365

Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu
    370   375   380

Leu Lys Asn Ser Ser Leu Ser Val Leu His Lys Leu Pro Arg Leu Glu
385   390   395   400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile
                405   410   415

Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys
            420   425   430

Ile Ser Pro Ser Glu Glu Ser Arg Glu Val Gly Phe Cys Pro Asn Ala
        435   440   445

Gln Thr Ser Val Asp Arg His Gly Pro Gln Val Leu Glu Ala Leu His
    450   455   460

Tyr Phe Arg Tyr Asp Glu Tyr Ala Arg Ser Cys Arg Phe Lys Asn Lys
465   470   475   480

Glu Pro Pro Ser Phe Leu Pro Leu Asn Ala Asp Cys His Ile Tyr Gly
                485   490   495

Gln Thr Leu Asp Leu Ser Arg Asn Asn Ile Phe Phe Ile Lys Pro Ser
            500   505   510

Asp Phe Gln His Leu Ser Phe Leu Lys Cys Leu Asn Leu Ser Gly Asn
        515   520   525

Thr Ile Gly Gln Thr Leu Asn Gly Ser Glu Leu Trp Pro Leu Arg Glu
    530   535   540

Leu Arg Tyr Leu Asp Phe Ser Asn Asn Arg Leu Asp Leu Leu Tyr Ser
545   550   555   560

Thr Ala Phe Glu Glu Leu Gln Ser Leu Glu Val Leu Asp Leu Ser Ser
                565   570   575

Asn Ser His Tyr Phe Gln Ala Glu Gly Ile Thr His Met Leu Asn Phe
            580   585   590

Thr Lys Lys Leu Arg Leu Leu Asp Lys Leu Met Met Asn Asp Asn Asp
        595   600   605

Ile Ser Thr Ser Ala Ser Arg Thr Met Glu Ser Asp Ser Leu Arg Ile

610 615 620
Leu Glu Phe Arg Gly Asn His Leu Asp Val Leu Trp Arg Ala Gly Asp
625 630 635 640

Asn Arg Tyr Leu Asp Phe Phe Lys Asn Leu Phe Asn Leu Glu Val Leu
645 650 655

Asp Ile Ser Arg Asn Ser Leu Asn Ser Leu Pro Pro Glu Val Phe Glu
660 665 670

Gly Met Pro Pro Asn Leu Lys Asn Leu Ser Leu Ala Lys Asn Gly Leu
675 680 685

Lys Ser Phe Phe Trp Asp Arg Leu Gln Leu Leu Lys His Leu Glu Ile
690 695 700

Leu Asp Leu Ser His Asn Gln Leu Thr Lys Val Pro Glu Arg Leu Ala
705 710 715 720

Asn Cys Ser Lys Ser Leu Thr Thr Leu Ile Leu Lys His Asn Gln Ile
725 730 735

Arg Gln Leu Thr Lys Tyr Phe Leu Glu Asp Ala Leu Gln Leu Arg Tyr
740 745 750

Leu Asp Ile Ser Ser Asn Lys Ile Gln Val Ile Gln Lys Thr Ser Phe
755 760 765

Pro Glu Asn Val Leu Asn Asn Leu Glu Met Leu Val Leu His His Asn
770 775 780

Arg Phe Leu Cys Asn Cys Asp Ala Val Trp Phe Val Trp Trp Val Asn
785 790 795 800

His Thr Asp Val Thr Ile Pro Tyr Leu Ala Thr Asp Val Thr Cys Val
805 810 815

Gly Pro Gly Ala His Lys Gly Gln Ser Val Ile Ser Leu Asp Leu Tyr
820 825 830

Thr Cys Glu Leu Asp Leu Thr Asn Leu Ile Leu Phe Ser Val Ser Ile
835 840 845

Ser Ser Val Leu Phe Leu Met Val Val Met Thr Thr Ser His Leu Phe
850 855 860

Phe Trp Asp Met Trp Tyr Ile Tyr Tyr Phe Trp Lys Ala Lys Ile Lys
865 870 875 880

Gly Tyr Gln His Leu Gln Ser Met Glu Ser Cys Tyr Asp Ala Phe Ile
885 890 895

Val Tyr Asp Thr Lys Asn Ser Ala Val Thr Glu Trp Val Leu Gln Glu
900 905 910

Leu Val Ala Lys Leu Glu Asp Pro Arg Glu Lys His Phe Asn Leu Cys
915 920 925

Leu Glu Glu Arg Asp Trp Leu Pro Gly Gln Pro Val Leu Glu Asn Leu
930 935 940

Ser Gln Ser Ile Gln Leu Ser Lys Lys Thr Val Phe Val Met Thr Gln

945 950 955 960
Lys Tyr Ala Lys Thr Glu Ser Phe Lys Met Ala Phe Tyr Leu Ser His
965 970 975

Gln Arg Leu Leu Asp Glu Lys Val Asp Val Ile Ile Leu Ile Phe Leu
980 985 990

Glu Lys Pro Leu Gln Lys Ser Lys Phe Leu Gln Leu Arg Lys Arg Leu
995 1000 1005

Cys Arg Ser Ser Val Leu Glu Trp Pro Ala Asn Pro Gln Ala His
1010 1015 1020

Pro Tyr Phe Trp Gln Cys Leu Lys Asn Ala Leu Thr Thr Asp Asn
1025 1030 1035

His Val Ala Tyr Ser Gln Met Phe Lys Glu Thr Val
1040 1045 1050

<210> 45
<211> 1050
<212> PRT
<213> murine

<400> 45

Met Val Phe Ser Met Trp Thr Arg Lys Arg Gln Ile Leu Ile Phe Leu
1 5 10 15

Asn Met Leu Leu Val Ser Arg Val Phe Gly Phe Arg Trp Phe Pro Lys
20 25 30

Thr Leu Pro Cys Glu Val Lys Val Asn Ile Pro Glu Ala His Val Ile
35 40 45

Val Asp Cys Thr Asp Lys His Leu Thr Glu Ile Pro Glu Gly Ile Pro
50 55 60

Thr Asn Thr Thr Asn Leu Thr Leu Thr Ile Asn His Ile Pro Ser Ile
65 70 75 80

Ser Pro Asp Ser Phe Arg Arg Leu Asn His Leu Glu Glu Ile Asp Leu
85 90 95

Arg Cys Asn Cys Val Pro Val Leu Leu Gly Ser Lys Ala Asn Val Cys
100 105 110

Thr Lys Arg Leu Gln Ile Arg Pro Gly Ser Phe Ser Gly Leu Ser Asp
115 120 125

Leu Lys Ala Leu Tyr Leu Asp Gly Asn Gln Leu Leu Glu Ile Pro Gln
130 135 140

Asp Leu Pro Ser Ser Leu His Leu Leu Ser Leu Glu Ala Asn Asn Ile
145 150 155 160

Phe Ser Ile Thr Lys Glu Asn Leu Thr Glu Leu Val Asn Ile Glu Thr
165 170 175

Leu Tyr Leu Gly Gln Asn Cys Tyr Tyr Arg Asn Pro Cys Asn Val Ser
180 185 190

Tyr Ser Ile Glu Lys Asp Ala Phe Leu Val Met Arg Asn Leu Lys Val
195 200 205

Leu Ser Leu Lys Asp Asn Asn Val Thr Ala Val Pro Thr Thr Leu Pro
210 215 220

Pro Asn Leu Leu Glu Leu Tyr Leu Tyr Asn Asn Ile Ile Lys Lys Ile
225 230 235 240

Gln Glu Asn Asp Phe Asn Asn Leu Asn Glu Leu Gln Val Leu Asp Leu
245 250 255

Ser Gly Asn Cys Pro Arg Cys Tyr Asn Val Pro Tyr Pro Cys Thr Pro
260 265 270

Cys Glu Asn Asn Ser Pro Leu Gln Ile His Asp Asn Ala Phe Asn Ser
275 280 285

Leu Thr Glu Leu Lys Val Leu Arg Leu His Ser Asn Ser Leu Gln His
290 295 300

Val Pro Pro Thr Trp Phe Lys Asn Met Arg Asn Leu Gln Glu Leu Asp
305 310 315 320

Leu Ser Gln Asn Tyr Leu Ala Arg Glu Ile Glu Glu Ala Lys Phe Leu
325 330 335

His Phe Leu Pro Asn Leu Val Glu Leu Asp Phe Ser Phe Asn Tyr Glu
340 345 350

Leu Gln Val Tyr His Ala Ser Ile Thr Leu Pro His Ser Leu Ser Ser
355 360 365

Leu Glu Asn Leu Lys Ile Leu Arg Val Lys Gly Tyr Val Phe Lys Glu
370 375 380

Leu Lys Asn Ser Ser Leu Ser Val Leu His Lys Leu Pro Arg Leu Glu
385 390 395 400

Val Leu Asp Leu Gly Thr Asn Phe Ile Lys Ile Ala Asp Leu Asn Ile
405 410 415

Phe Lys His Phe Glu Asn Leu Lys Leu Ile Asp Leu Ser Val Asn Lys
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agaagatgga gtatttgaaa cgctgacaaa tttggagttg ctatcactat ctttcaattc 840
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ccagatcaaa tacattagtg aagaagattt caagggattg ataaatttaa cattactaga 960
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attgtccgac ttggaagttc tagatctcag ctataattca cactatttca gaatagcagg 1920
cgtaacacat catctagaat ttattcaaaa tttcacaaat ctaaaagttt taaacttgag 1980
ccacaacaac atttatactt taacagataa gtataacctg gaaagcaagt ccctggtaga 2040

attagttttc agtggcaatc gccttgacat tttgtggaat gatgatgaca acaggtatat 2100
ctccattttc aaaggtctca agaatctgac acgtctggat ttatccctta ataggctgaa 2160
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tgataatatg ttaaagtttt ttaactggac attactccag cagtttcctc gtctcgagtt 2280
gcttgactta cgtggaaaca aactactctt tttaactgat agcctatctg actttacatc 2340
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ggatgtgatt atatttatcc tgctggagcc agtgttacag cattctcagt atttgaggct 3180
acggcagcgg atctgtaaga gctccatcct ccagtggcct gacaacccga aggcagaagg 3240
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<212> PRT
<213> Homo sapiens

<400> 50

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Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg
20 25 30

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Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
        35                  40                  45

Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
    50                  55                  60

Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
65                  70                  75                  80

Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
                85                  90                  95

Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
            100                 105                 110

Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
        115                 120                 125

Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
    130                 135                 140

Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn
145                 150                 155                 160

Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr
                165                 170                 175

Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
            180                 185                 190

Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
        195                 200                 205

Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
    210                 215                 220

Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
225                 230                 235                 240

Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
                245                 250                 255

Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
            260                 265                 270

Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
        275                 280                 285

Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
    290                 295                 300

Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
305                 310                 315                 320

Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
                325                 330                 335

Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
            340                 345                 350

Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser
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355 360 365
Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
370 375 380

Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn
385 390 395 400

Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
405 410 415

Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
420 425 430

Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
435 440 445

Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
450 455 460

Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala
465 470 475 480

Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile
485 490 495

Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu
500 505 510

Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala
515 520 525

Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe
530 535 540

Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp
545 550 555 560

Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His
565 570 575

Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser
580 585 590

His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys
595 600 605

Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp
610 615 620

Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn
625 630 635 640

Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn
645 650 655

Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn
660 665 670

Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro
675 680 685

Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr

690 695 700
Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser
705 710 715 720

His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser
725 730 735

Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn
740 745 750

Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu
755 760 765

Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg
770 775 780

Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp
785 790 795 800

Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser
805 810 815

Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe
820 825 830

Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala
835 840 845

His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu
850 855 860

Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr
865 870 875 880

Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp
885 890 895

Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn
900 905 910

Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile
915 920 925

Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe
930 935 940

Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe
945 950 955 960

Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile
965 970 975

Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
980 985 990

Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro
995 1000 1005

Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu
1010 1015 1020

Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val Asp Ser Ile

1025 1030 1035
Lys Gln Tyr
1040

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<212> PRT
<213> Homo sapiens

<400> 51

Met Lys Glu Ser Ser Leu Gln Asn Ser Ser Cys Ser Leu Gly Lys Glu
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Thr Lys Lys Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile
20 25 30

Phe Leu Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe
35 40 45

Ser Arg Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile
50 55 60

Ala Glu Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly
65 70 75 80

Lys Tyr Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile
85 90 95

Thr Asn Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu
100 105 110

Asn His Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln
115 120 125

Ser Asn Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn
130 135 140

Leu Arg Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser
145 150 155 160

Gly Leu Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile
165 170 175

Tyr Asn Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn
180 185 190

Leu Tyr Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr
195 200 205

Asn Ile Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu
210 215 220

Ser Leu Ser Phe Asn Ser Leu Ser His Val Ser Pro Lys Leu Pro Ser
225 230 235 240

Ser Leu Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser
245 250 255

Glu Glu Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser
260 265 270

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Gly Asn Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys
        275                 280                 285

Asp Gly Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu
    290                 295                 300

Thr Gln Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile
305                 310                 315                 320

Asn Ala Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu
                325                 330                 335

Glu Phe Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr
            340                 345                 350

Met Leu Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys
        355                 360                 365

Gly Ser Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Pro
    370                 375                 380

Leu Ser Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu
385                 390                 395                 400

Arg Glu Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr
                405                 410                 415

Ile Asn Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe
            420                 425                 430

Gln Asn Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile
        435                 440                 445

Ser Pro Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser
    450                 455                 460

Phe Gln Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp
465                 470                 475                 480

Pro His Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln
                485                 490                 495

Cys Ala Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe
            500                 505                 510

Phe Ile Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu
        515                 520                 525

Asn Leu Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe
    530                 535                 540

Ser Ala Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu
545                 550                 555                 560

Asp Phe Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val
                565                 570                 575

Leu Asp Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr
            580                 585                 590

His His Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn
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595 600 605
Leu Ser His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu
610 615 620

Ser Lys Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile
625 630 635 640

Leu Trp Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu
645 650 655

Lys Asn Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile
660 665 670

Pro Asn Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His
675 680 685

Ile Asn Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln
690 695 700

Phe Pro Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe
705 710 715 720

Leu Thr Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu
725 730 735

Leu Ser His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu
740 745 750

Val Ser Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr
755 760 765

Ile Asn Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met
770 775 780

Leu Glu Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp
785 790 795 800

Phe Arg Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu
805 810 815

Val Asp Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile
820 825 830

Val Ser Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile
835 840 845

Leu Phe Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala
850 855 860

Leu Ala His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val
865 870 875 880

Cys Leu Ala Lys Ile Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr
885 890 895

Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr
900 905 910

Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp
915 920 925

Lys Asn Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu

```
    930                 935                 940
Ala Ile Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr
945                 950                 955                 960

Val Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr
                965                 970                 975

Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val
            980                 985                 990

Ile Ile Phe Ile Leu Leu Glu Pro  Val Leu Gln His Ser  Gln Tyr Leu
        995                 1000                 1005

Arg Leu  Arg Gln Arg Ile Cys  Lys Ser Ser Ile Leu  Gln Trp Pro
    1010                 1015                 1020

Asp Asn  Pro Lys Ala Glu Gly  Leu Phe Trp Gln Thr  Leu Arg Asn
    1025                 1030                 1035

Val Val  Leu Thr Glu Asn Asp  Ser Arg Tyr Asn Asn  Met Tyr Val
    1040                 1045                 1050

Asp Ser  Ile Lys Gln Tyr
    1055


<210>  52
<211>  1041
<212>  PRT
<213>  Homo sapiens

<400>  52

Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu
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Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg
            20                  25                  30

Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
        35                  40                  45

Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
    50                  55                  60

Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
65                  70                  75                  80

Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
                85                  90                  95

Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
            100                 105                 110

Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
        115                 120                 125

Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
    130                 135                 140

Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn
145                 150                 155                 160
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Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr
165 170 175

Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
180 185 190

Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
195 200 205

Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
210 215 220

Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
225 230 235 240

Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
245 250 255

Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
260 265 270

Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
275 280 285

Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
290 295 300

Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
305 310 315 320

Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
325 330 335

Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
340 345 350

Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser
355 360 365

Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
370 375 380

Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn
385 390 395 400

Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
405 410 415

Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
420 425 430

Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
435 440 445

Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
450 455 460

Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln Cys Ala
465 470 475 480

Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile

485 490 495
Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu
500 505 510

Ser Ala Asn Ser Asn Ala Gln Val Leu Ser Gly Thr Glu Phe Ser Ala
515 520 525

Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu Asp Phe
530 535 540

Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val Leu Asp
545 550 555 560

Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr His His
565 570 575

Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser
580 585 590

His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys
595 600 605

Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp
610 615 620

Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn
625 630 635 640

Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn
645 650 655

Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn
660 665 670

Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro
675 680 685

Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr
690 695 700

Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser
705 710 715 720

His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser
725 730 735

Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn
740 745 750

Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu
755 760 765

Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg
770 775 780

Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp
785 790 795 800

Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser
805 810 815

Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe

820 825 830
Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala
835 840 845

His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu
850 855 860

Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr
865 870 875 880

Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp
885 890 895

Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn
900 905 910

Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile
915 920 925

Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe
930 935 940

Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe
945 950 955 960

Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile
965 970 975

Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
980 985 990

Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro Asp Asn Pro
995 1000 1005

Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn Val Val Leu
1010 1015 1020

Thr Glu Asn Asp Ser Arg Tyr Asn Asn Met Tyr Val Asp Ser Ile
1025 1030 1035

Lys Gln Tyr
1040

<210> 53
<211> 1041
<212> PRT
<213> Homo sapiens

<400> 53

Met Glu Asn Met Phe Leu Gln Ser Ser Met Leu Thr Cys Ile Phe Leu
1 5 10 15

Leu Ile Ser Gly Ser Cys Glu Leu Cys Ala Glu Glu Asn Phe Ser Arg
20 25 30

Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile Ala Glu
35 40 45

Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly Lys Tyr
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Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile Thr Asn
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Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu Asn His
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Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln Ser Asn
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Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn Leu Arg
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Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser Gly Leu
130 135 140

Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile Tyr Asn
145 150 155 160

Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn Leu Tyr
165 170 175

Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr Asn Ile
180 185 190

Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu Ser Leu
195 200 205

Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser Ser Leu
210 215 220

Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser Glu Glu
225 230 235 240

Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn
245 250 255

Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys Asp Gly
260 265 270

Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu Thr Gln
275 280 285

Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile Asn Ala
290 295 300

Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu Glu Phe
305 310 315 320

Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr Met Leu
325 330 335

Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys Gly Ser
340 345 350

Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu Leu Ser
355 360 365

Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu Arg Glu
370 375 380

Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr Ile Asn

385 390 395 400
Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe Gln Asn
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Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile Ser Pro
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Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser Phe Gln
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Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp Pro His
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465 470 475 480

Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe Phe Ile
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Gly Pro Asn Gln Phe Glu Asn Leu Pro Asp Ile Ala Cys Leu Asn Leu
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Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn Leu Ser
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His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu Ser Lys
595 600 605

Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile Leu Trp
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Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu Lys Asn
625 630 635 640

Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile Pro Asn
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Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His Ile Asn
660 665 670

Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln Phe Pro
675 680 685

Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe Leu Thr
690 695 700

Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu Leu Ser
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His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu Val Ser

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Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr Ile Asn
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Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met Leu Glu
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Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp Phe Arg
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Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu Val Asp
785                     790                     795                     800

Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile Val Ser
                805                     810                     815

Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile Leu Phe
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Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala Leu Ala
        835                     840                     845

His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val Cys Leu
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Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr Phe Tyr
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Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr Asp Trp
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Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp Lys Asn
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Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu Ala Ile
        915                     920                     925

Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr Val Phe
    930                     935                     940

Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr Ala Phe
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Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val Ile Ile
                965                     970                     975

Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu Arg Leu
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Arg Gln Arg Ile Cys Lys Ser Ser  Ile Leu Gln Trp Pro  Asp Asn Pro
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Lys Ala  Glu Gly Leu Phe Trp  Gln Thr Leu Arg Asn  Val Val Leu
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35 40 45

Ser Arg Ser Tyr Pro Cys Asp Glu Lys Lys Gln Asn Asp Ser Val Ile
50 55 60

Ala Glu Cys Ser Asn Arg Arg Leu Gln Glu Val Pro Gln Thr Val Gly
65 70 75 80

Lys Tyr Val Thr Glu Leu Asp Leu Ser Asp Asn Phe Ile Thr His Ile
85 90 95

Thr Asn Glu Ser Phe Gln Gly Leu Gln Asn Leu Thr Lys Ile Asn Leu
100 105 110

Asn His Asn Pro Asn Val Gln His Gln Asn Gly Asn Pro Gly Ile Gln
115 120 125

Ser Asn Gly Leu Asn Ile Thr Asp Gly Ala Phe Leu Asn Leu Lys Asn
130 135 140

Leu Arg Glu Leu Leu Leu Glu Asp Asn Gln Leu Pro Gln Ile Pro Ser
145 150 155 160

Gly Leu Pro Glu Ser Leu Thr Glu Leu Ser Leu Ile Gln Asn Asn Ile
165 170 175

Tyr Asn Ile Thr Lys Glu Gly Ile Ser Arg Leu Ile Asn Leu Lys Asn
180 185 190

Leu Tyr Leu Ala Trp Asn Cys Tyr Phe Asn Lys Val Cys Glu Lys Thr
195 200 205

Asn Ile Glu Asp Gly Val Phe Glu Thr Leu Thr Asn Leu Glu Leu Leu
210 215 220

Ser Leu Ser Phe Asn Ser Leu Ser His Val Pro Pro Lys Leu Pro Ser
225 230 235 240

Ser Leu Arg Lys Leu Phe Leu Ser Asn Thr Gln Ile Lys Tyr Ile Ser
245 250 255

Glu Glu Asp Phe Lys Gly Leu Ile Asn Leu Thr Leu Leu Asp Leu Ser
260 265 270

Gly Asn Cys Pro Arg Cys Phe Asn Ala Pro Phe Pro Cys Val Pro Cys
275 280 285

Asp Gly Gly Ala Ser Ile Asn Ile Asp Arg Phe Ala Phe Gln Asn Leu
290 295 300

Thr Gln Leu Arg Tyr Leu Asn Leu Ser Ser Thr Ser Leu Arg Lys Ile
305 310 315 320

Asn Ala Ala Trp Phe Lys Asn Met Pro His Leu Lys Val Leu Asp Leu
325 330 335

Glu Phe Asn Tyr Leu Val Gly Glu Ile Ala Ser Gly Ala Phe Leu Thr
340 345 350

Met Leu Pro Arg Leu Glu Ile Leu Asp Leu Ser Phe Asn Tyr Ile Lys
355 360 365

Gly Ser Tyr Pro Gln His Ile Asn Ile Ser Arg Asn Phe Ser Lys Leu
370 375 380

Leu Ser Leu Arg Ala Leu His Leu Arg Gly Tyr Val Phe Gln Glu Leu
385 390 395 400

Arg Glu Asp Asp Phe Gln Pro Leu Met Gln Leu Pro Asn Leu Ser Thr
405 410 415

Ile Asn Leu Gly Ile Asn Phe Ile Lys Gln Ile Asp Phe Lys Leu Phe
420 425 430

Gln Asn Phe Ser Asn Leu Glu Ile Ile Tyr Leu Ser Glu Asn Arg Ile
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Ser Pro Leu Val Lys Asp Thr Arg Gln Ser Tyr Ala Asn Ser Ser Ser
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Phe Gln Arg His Ile Arg Lys Arg Arg Ser Thr Asp Phe Glu Phe Asp
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Pro His Ser Asn Phe Tyr His Phe Thr Arg Pro Leu Ile Lys Pro Gln
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Cys Ala Ala Tyr Gly Lys Ala Leu Asp Leu Ser Leu Asn Ser Ile Phe
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Ser Ala Ile Pro His Val Lys Tyr Leu Asp Leu Thr Asn Asn Arg Leu
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Asp Phe Asp Asn Ala Ser Ala Leu Thr Glu Leu Ser Asp Leu Glu Val
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Leu Asp Leu Ser Tyr Asn Ser His Tyr Phe Arg Ile Ala Gly Val Thr
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His His Leu Glu Phe Ile Gln Asn Phe Thr Asn Leu Lys Val Leu Asn
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Leu Ser His Asn Asn Ile Tyr Thr Leu Thr Asp Lys Tyr Asn Leu Glu

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Ser Lys Ser Leu Val Glu Leu Val Phe Ser Gly Asn Arg Leu Asp Ile
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Leu Trp Asn Asp Asp Asp Asn Arg Tyr Ile Ser Ile Phe Lys Gly Leu
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Lys Asn Leu Thr Arg Leu Asp Leu Ser Leu Asn Arg Leu Lys His Ile
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Pro Asn Glu Ala Phe Leu Asn Leu Pro Ala Ser Leu Thr Glu Leu His
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Ile Asn Asp Asn Met Leu Lys Phe Phe Asn Trp Thr Leu Leu Gln Gln
690 695 700

Phe Pro Arg Leu Glu Leu Leu Asp Leu Arg Gly Asn Lys Leu Leu Phe
705 710 715 720

Leu Thr Asp Ser Leu Ser Asp Phe Thr Ser Ser Leu Arg Thr Leu Leu
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Leu Ser His Asn Arg Ile Ser His Leu Pro Ser Gly Phe Leu Ser Glu
740 745 750

Val Ser Ser Leu Lys His Leu Asp Leu Ser Ser Asn Leu Leu Lys Thr
755 760 765

Ile Asn Lys Ser Ala Leu Glu Thr Lys Thr Thr Thr Lys Leu Ser Met
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Leu Glu Leu His Gly Asn Pro Phe Glu Cys Thr Cys Asp Ile Gly Asp
785 790 795 800

Phe Arg Arg Trp Met Asp Glu His Leu Asn Val Lys Ile Pro Arg Leu
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Val Asp Val Ile Cys Ala Ser Pro Gly Asp Gln Arg Gly Lys Ser Ile
820 825 830

Val Ser Leu Glu Leu Thr Thr Cys Val Ser Asp Val Thr Ala Val Ile
835 840 845

Leu Phe Phe Phe Thr Phe Phe Ile Thr Thr Met Val Met Leu Ala Ala
850 855 860

Leu Ala His His Leu Phe Tyr Trp Asp Val Trp Phe Ile Tyr Asn Val
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Cys Leu Ala Lys Val Lys Gly Tyr Arg Ser Leu Ser Thr Ser Gln Thr
885 890 895

Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys Asp Ala Ser Val Thr
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Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu Glu Glu Ser Arg Asp
915 920 925

Lys Asn Val Leu Leu Cys Leu Glu Glu Arg Asp Trp Asp Pro Gly Leu
930 935 940

Ala Ile Ile Asp Asn Leu Met Gln Ser Ile Asn Gln Ser Lys Lys Thr

945 950 955 960
Val Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser Trp Asn Phe Lys Thr
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Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp Glu Asn Met Asp Val
980 985 990

Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln His Ser Gln Tyr Leu
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Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile Leu Gln Trp Pro
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Asp Asn Pro Lys Ala Glu Gly Leu Phe Trp Gln Thr Leu Arg Asn
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Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys
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115 120 125

Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu
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Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn
145 150 155 160

Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn
165 170 175

Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe
180 185 190

Lys Asn Leu Ile His Leu Lys Val Leu Ser Leu Ser Phe Asn Asn Leu
195 200 205

Phe Tyr Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu
210 215 220

Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu
225 230 235 240

Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr
245 250 255

Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His
260 265 270

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Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn
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Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn
    290                 295                 300

Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln
305                 310                 315                 320

Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile
                325                 330                 335

Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile
            340                 345                 350

Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His
        355                 360                 365

Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His
    370                 375                 380

Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe
385                 390                 395                 400

Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp
                405                 410                 415

Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr
            420                 425                 430

Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp
        435                 440                 445

Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro
    450                 455                 460

Leu Ile Lys Pro Gln Cys Thr Ala Tyr Gly Lys Ala Leu Asp Leu Ser
465                 470                 475                 480

Leu Asn Asn Ile Phe Ile Ile Gly Lys Ser Gln Phe Glu Gly Phe Gln
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Asp Ile Ala Cys Leu Asn Leu Ser Phe Asn Ala Asn Thr Gln Val Phe
            500                 505                 510

Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu
        515                 520                 525

Thr Asn Asn Arg Leu Asp Phe Asp Asp Asn Asn Ala Phe Ser Asp Leu
    530                 535                 540

His Asp Leu Glu Val Leu Asp Leu Ser His Asn Ala His Tyr Phe Ser
545                 550                 555                 560

Ile Ala Gly Val Thr His Arg Leu Gly Phe Ile Gln Asn Leu Ile Asn
                565                 570                 575

Leu Arg Val Leu Asn Leu Ser His Asn Gly Ile Tyr Thr Leu Thr Glu
            580                 585                 590

Glu Ser Glu Leu Lys Ser Ile Ser Leu Lys Glu Leu Val Phe Ser Gly
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Asn Arg Leu Asp His Leu Trp Asn Ala Asn Asp Gly Lys Tyr Trp Ser
610 615 620

Ile Phe Lys Ser Leu Gln Asn Leu Ile Arg Leu Asp Leu Ser Tyr Asn
625 630 635 640

Asn Leu Gln Gln Ile Pro Asn Gly Ala Phe Leu Asn Leu Pro Gln Ser
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Leu Gln Glu Leu Leu Ile Ser Gly Asn Lys Leu Arg Phe Phe Asn Trp
660 665 670

Thr Leu Leu Gln Tyr Phe Pro His Leu His Leu Leu Asp Leu Ser Arg
675 680 685

Asn Glu Leu Tyr Phe Leu Pro Asn Cys Leu Ser Lys Phe Ala His Ser
690 695 700

Leu Glu Thr Leu Leu Leu Ser His Asn His Phe Ser His Leu Pro Ser
705 710 715 720

Gly Phe Leu Ser Glu Ala Arg Asn Leu Val His Leu Asp Leu Ser Phe
725 730 735

Asn Thr Ile Lys Met Ile Asn Lys Ser Ser Leu Gln Thr Lys Met Lys
740 745 750

Thr Asn Leu Ser Ile Leu Glu Leu His Gly Asn Tyr Phe Asp Cys Thr
755 760 765

Cys Asp Ile Ser Asp Phe Arg Ser Trp Leu Asp Glu Asn Leu Asn Ile
770 775 780

Thr Ile Pro Lys Leu Val Asn Val Ile Cys Ser Asn Pro Gly Asp Gln
785 790 795 800

Lys Ser Lys Ser Ile Met Ser Leu Asp Leu Thr Thr Cys Val Ser Asp
805 810 815

Thr Thr Ala Ala Val Leu Phe Phe Leu Thr Phe Leu Thr Thr Ser Met
820 825 830

Val Met Leu Ala Ala Leu Val His His Leu Phe Tyr Trp Asp Val Trp
835 840 845

Phe Ile Tyr His Met Cys Ser Ala Lys Leu Lys Gly Tyr Arg Thr Ser
850 855 860

Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys
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Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu
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Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp
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Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn
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Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser

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Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp
945 950 955 960

Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln
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Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile
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Cys Asn His Arg Gln Leu His Glu Val Pro Gln Thr Ile Gly Lys Tyr
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Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys
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Glu Ser Phe Gln Lys Leu Gln Asn Leu Thr Lys Ile Asp Leu Asn His
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Asn Ala Lys Gln Gln His Pro Asn Glu Asn Lys Asn Gly Met Asn Ile
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Thr Glu Gly Ala Leu Leu Ser Leu Arg Asn Leu Thr Val Leu Leu Leu
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Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu
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Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn
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Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn
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Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe
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Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu
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Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr
                245                 250                 255

Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His
            260                 265                 270

Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn
        275                 280                 285

Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn
    290                 295                 300

Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln
305                 310                 315                 320

Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile
                325                 330                 335

Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile
            340                 345                 350

Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His
        355                 360                 365

Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His
    370                 375                 380

Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe
385                 390                 395                 400

Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp
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Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr
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Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp
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Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro
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Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu
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Ile Ala Gly Val Thr His Arg Leu Gly Phe Ile Gln Asn Leu Ile Asn
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Leu Arg Val Leu Asn Leu Ser His Asn Gly Ile Tyr Thr Leu Thr Glu
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Glu Ser Glu Leu Lys Ser Ile Ser Leu Lys Glu Leu Val Phe Ser Gly
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Asn Arg Leu Asp His Leu Trp Asn Ala Asn Asp Gly Lys Tyr Trp Ser
610 615 620

Ile Phe Lys Ser Leu Gln Asn Leu Ile Arg Leu Asp Leu Ser Tyr Asn
625 630 635 640

Asn Leu Gln Gln Ile Pro Asn Gly Ala Phe Leu Asn Leu Pro Gln Ser
645 650 655

Leu Gln Glu Leu Leu Ile Ser Gly Asn Lys Leu Arg Phe Phe Asn Trp
660 665 670

Thr Leu Leu Gln Tyr Phe Pro His Leu His Leu Leu Asp Leu Ser Arg
675 680 685

Asn Glu Leu Tyr Phe Leu Pro Asn Cys Leu Ser Lys Phe Ala His Ser
690 695 700

Leu Glu Thr Leu Leu Leu Ser His Asn His Phe Ser His Leu Pro Ser
705 710 715 720

Gly Phe Leu Ser Glu Ala Arg Asn Leu Val His Leu Asp Leu Ser Phe
725 730 735

Asn Thr Ile Lys Met Ile Asn Lys Ser Ser Leu Gln Thr Lys Met Lys
740 745 750

Thr Asn Leu Ser Ile Leu Glu Leu His Gly Asn Tyr Phe Asp Cys Thr
755 760 765

Cys Asp Ile Ser Asp Phe Arg Ser Trp Leu Asp Glu Asn Leu Asn Ile
770 775 780

Thr Ile Pro Lys Leu Val Asn Val Ile Cys Ser Asn Pro Gly Asp Gln
785 790 795 800

Lys Ser Lys Ser Ile Met Ser Leu Asp Leu Thr Thr Cys Val Ser Asp
805 810 815

Thr Thr Ala Ala Val Leu Phe Phe Leu Thr Phe Leu Thr Thr Ser Met
820 825 830

Val Met Leu Ala Ala Leu Val His His Leu Phe Tyr Trp Asp Val Trp
835 840 845

Phe Ile Tyr His Met Cys Ser Ala Lys Leu Lys Gly Tyr Arg Thr Ser

850 855 860
Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys
865 870 875 880

Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu
885 890 895

Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp
900 905 910

Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn
915 920 925

Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser
930 935 940

Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp
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Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln
965 970 975

Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile
980 985 990

Leu Gln Trp Pro Asn Asn Pro Lys Ala Glu Asn Leu Phe Trp Gln Ser
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Cys Asn His Arg Gln Leu His Glu Val Pro Gln Thr Ile Gly Lys Tyr
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Val Thr Asn Ile Asp Leu Ser Asp Asn Ala Ile Thr His Ile Thr Lys
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Glu Ser Phe Gln Lys Leu Gln Asn Leu Thr Lys Ile Asp Leu Asn His
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Asn Ala Lys Gln Gln His Pro Asn Glu Asn Lys Asn Gly Met Asn Ile
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Thr Glu Gly Ala Leu Leu Ser Leu Arg Asn Leu Thr Val Leu Leu Leu
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Glu Asp Asn Gln Leu Tyr Thr Ile Pro Ala Gly Leu Pro Glu Ser Leu
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Lys Glu Leu Ser Leu Ile Gln Asn Asn Ile Phe Gln Val Thr Lys Asn
145 150 155 160

Asn Thr Phe Gly Leu Arg Asn Leu Glu Arg Leu Tyr Leu Gly Trp Asn
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Cys Tyr Phe Lys Cys Asn Gln Thr Phe Lys Val Glu Asp Gly Ala Phe
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Lys Asn Leu Ile His Leu Lys Val Leu Ser Leu Ser Phe Asn Asn Leu
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Phe Tyr Val Pro Pro Lys Leu Pro Ser Ser Leu Arg Lys Leu Phe Leu
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Ser Asn Ala Lys Ile Met Asn Ile Thr Gln Glu Asp Phe Lys Gly Leu
225 230 235 240

Glu Asn Leu Thr Leu Leu Asp Leu Ser Gly Asn Cys Pro Arg Cys Tyr
245 250 255

Asn Ala Pro Phe Pro Cys Thr Pro Cys Lys Glu Asn Ser Ser Ile His
260 265 270

Ile His Pro Leu Ala Phe Gln Ser Leu Thr Gln Leu Leu Tyr Leu Asn
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Leu Ser Ser Thr Ser Leu Arg Thr Ile Pro Ser Thr Trp Phe Glu Asn
290 295 300

Leu Ser Asn Leu Lys Glu Leu His Leu Glu Phe Asn Tyr Leu Val Gln
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Glu Ile Ala Ser Gly Ala Phe Leu Thr Lys Leu Pro Ser Leu Gln Ile
325 330 335

Leu Asp Leu Ser Phe Asn Phe Gln Tyr Lys Glu Tyr Leu Gln Phe Ile
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Asn Ile Ser Ser Asn Phe Ser Lys Leu Arg Ser Leu Lys Lys Leu His
355 360 365

Leu Arg Gly Tyr Val Phe Arg Glu Leu Lys Lys Lys His Phe Glu His
370 375 380

Leu Gln Ser Leu Pro Asn Leu Ala Thr Ile Asn Leu Gly Ile Asn Phe
385 390 395 400

Ile Glu Lys Ile Asp Phe Lys Ala Phe Gln Asn Phe Ser Lys Leu Asp
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Val Ile Tyr Leu Ser Gly Asn Arg Ile Ala Ser Val Leu Asp Gly Thr
420 425 430

Asp Tyr Ser Ser Trp Arg Asn Arg Leu Arg Lys Pro Leu Ser Thr Asp

435 440 445
Asp Asp Glu Phe Asp Pro His Val Asn Phe Tyr His Ser Thr Lys Pro
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Leu Asn Asn Ile Phe Ile Ile Gly Lys Ser Gln Phe Glu Gly Phe Gln
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Asp Ile Ala Cys Leu Asn Leu Ser Phe Asn Ala Asn Thr Gln Val Phe
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Asn Gly Thr Glu Phe Ser Ser Met Pro His Ile Lys Tyr Leu Asp Leu
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Thr Asn Asn Arg Leu Asp Phe Asp Asp Asn Asn Ala Phe Ser Asp Leu
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His Asp Leu Glu Val Leu Asp Leu Ser His Asn Ala His Tyr Phe Ser
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Ile Ala Gly Val Thr His Arg Leu Gly Phe Ile Gln Asn Leu Ile Asn
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Leu Arg Val Leu Asn Leu Ser His Asn Gly Ile Tyr Thr Leu Thr Glu
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Glu Ser Glu Leu Lys Ser Ile Ser Leu Lys Glu Leu Val Phe Ser Gly
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Asn Arg Leu Asp His Leu Trp Asn Ala Asn Asp Gly Lys Tyr Trp Ser
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Ile Phe Lys Ser Leu Gln Asn Leu Ile Arg Leu Asp Leu Ser Tyr Asn
625 630 635 640

Asn Leu Gln Gln Ile Pro Asn Gly Ala Phe Leu Asn Leu Pro Gln Ser
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Leu Gln Glu Leu Leu Ile Ser Gly Asn Lys Leu Arg Phe Phe Asn Trp
660 665 670

Thr Leu Leu Gln Tyr Phe Pro His Leu His Leu Leu Asp Leu Ser Arg
675 680 685

Asn Glu Leu Tyr Phe Leu Pro Asn Cys Leu Ser Lys Phe Ala His Ser
690 695 700

Leu Glu Thr Leu Leu Leu Ser His Asn His Phe Ser His Leu Pro Ser
705 710 715 720

Gly Phe Leu Ser Glu Ala Arg Asn Leu Val His Leu Asp Leu Ser Phe
725 730 735

Asn Thr Ile Lys Met Ile Asn Lys Ser Ser Leu Gln Thr Lys Met Lys
740 745 750

Thr Asn Leu Ser Ile Leu Glu Leu His Gly Asn Tyr Phe Asp Cys Thr
755 760 765

Cys Asp Ile Ser Asp Phe Arg Ser Trp Leu Asp Glu Asn Leu Asn Ile

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    770                 775                 780
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Lys Ser Lys Ser Ile Met Ser Leu Asp Leu Thr Thr Cys Val Ser Asp
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Thr Thr Ala Ala Val Leu Phe Phe Leu Thr Phe Leu Thr Thr Ser Met
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Val Met Leu Ala Ala Leu Val His His Leu Phe Tyr Trp Asp Val Trp
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Phe Ile Tyr His Met Cys Ser Ala Lys Leu Lys Gly Tyr Arg Thr Ser
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Ser Thr Ser Gln Thr Phe Tyr Asp Ala Tyr Ile Ser Tyr Asp Thr Lys
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Asp Ala Ser Val Thr Asp Trp Val Ile Asn Glu Leu Arg Tyr His Leu
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Glu Glu Ser Glu Asp Lys Ser Val Leu Leu Cys Leu Glu Glu Arg Asp
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Trp Asp Pro Gly Leu Pro Ile Ile Asp Asn Leu Met Gln Ser Ile Asn
        915                 920                 925

Gln Ser Lys Lys Thr Ile Phe Val Leu Thr Lys Lys Tyr Ala Lys Ser
    930                 935                 940

Trp Asn Phe Lys Thr Ala Phe Tyr Leu Ala Leu Gln Arg Leu Met Asp
945                 950                 955                 960

Glu Asn Met Asp Val Ile Ile Phe Ile Leu Leu Glu Pro Val Leu Gln
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Tyr Ser Gln Tyr Leu Arg Leu Arg Gln Arg Ile Cys Lys Ser Ser Ile
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Leu Gln Trp Pro Asn Asn Pro Lys  Ala Glu Asn Leu Phe  Trp Gln Ser
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Leu Lys  Asn Val Val Leu Thr  Glu Asn Asp Ser Arg  Tyr Asp Asp
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cctgggtacc ttgcctgcct tcctaccctg tgagctccag ccccacggcc tggtgaactg 240
caactggctg ttcctgaagt ctgtgcccca cttctccatg gcagcacccc gtggcaatgt 300
caccagcctt tccttgtcct ccaaccgcat ccaccacctc catgattctg actttgccca 360

cctgcccagc ctgcggcatc tcaacctcaa gtggaactgc ccgccggttg gcctcagccc 420
catgcacttc ccctgccaca tgaccatcga gcccagcacc ttcttggctg tgcccaccct 480

ggaagagcta aacctgagct acaacaacat catgactgtg cctgcgctgc ccaaatccct 540

catatccctg tccctcagcc ataccaacat cctgatgcta gactctgcca gcctcgccgg 600

cctgcatgcc ctgcgcttcc tattcatgga cggcaactgt tattacaaga acccctgcag 660

gcaggcactg gaggtggccc cgggtgccct ccttggcctg ggcaacctca cccacctgtc 720

actcaagtac aacaacctca ctgtggtgcc ccgcaacctg ccttccagcc tggagtatct 780

gctgttgtcc tacaaccgca tcgtcaaact ggcgcctgag gacctggcca atctgaccgc 840

cctgcgtgtg ctcgatgtgg gcggaaattg ccgccgctgc gaccacgctc ccaacccctg 900

catggagtgc cctcgtcact tcccccagct acatcccgat accttcagcc acctgagccg 960

tcttgaaggc ctggtgttga aggacagttc tctctcctgg ctgaatgcca gttggttccg 1020

tgggctggga aacctccgag tgctggacct gagtgagaac ttcctctaca aatgcatcac 1080

taaaaccaag gccttccagg gcctaacaca gctgcgcaag cttaacctgt ccttcaatta 1140

ccaaaagagg gtgtcctttg cccacctgtc tctggcccct tccttcggga gcctggtcgc 1200

cctgaaggag ctggacatgc acggcatctt cttccgctca ctcgatgaga ccacgctccg 1260

gccactggcc cgcctgccca tgctccagac tctgcgtctg cagatgaact tcatcaacca 1320

ggcccagctc ggcatcttca gggccttccc tggcctgcgc tacgtggacc tgtcggacaa 1380

ccgcatcagc ggagcttcgg agctgacagc caccatgggg gaggcagatg gaggggagaa 1440

ggtctggctg cagcctgggg accttgctcc ggccccagtg gacactccca gctctgaaga 1500

cttcaggccc aactgcagca ccctcaactt caccttggat ctgtcacgga acaacctggt 1560

gaccgtgcag ccggagatgt ttgcccagct ctcgcacctg cagtgcctgc gcctgagcca 1620

caactgcatc tcgcaggcag tcaatggctc ccagttcctg ccgctgaccg gtctgcaggt 1680

gctagacctg tcccacaata agctggacct ctaccacgag cactcattca cggagctacc 1740

acgactggag gccctggacc tcagctacaa cagccagccc tttggcatgc agggcgtggg 1800

ccacaacttc agcttcgtgg ctcacctgcg caccctgcgc cacctcagcc tggcccacaa 1860

caacatccac agccaagtgt cccagcagct ctgcagtacg tcgctgcggg ccctggactt 1920

cagcggcaat gcactgggcc atatgtgggc cgagggagac ctctatctgc acttcttcca 1980

aggcctgagc ggtttgatct ggctggactt gtcccagaac cgcctgcaca ccctcctgcc 2040

ccaaaccctg cgcaacctcc ccaagagcct acaggtgctg cgtctccgtg acaattacct 2100

ggccttcttt aagtggtgga gcctccactt cctgcccaaa ctggaagtcc tcgacctggc 2160

aggaaaccag ctgaaggccc tgaccaatgg cagcctgcct gctggcaccc ggctccggag 2220

gctggatgtc agctgcaaca gcatcagctt cgtggccccc ggcttctttt ccaaggccaa 2280

ggagctgcga gagctcaacc ttagcgccaa cgccctcaag acagtggacc actcctggtt 2340

tgggcccctg gcgagtgccc tgcaaatact agatgtaagc gccaaccctc tgcactgcgc 2400

ctgtggggcg gcctttatgg acttcctgct ggaggtgcag gctgccgtgc ccggtctgcc 2460

cagccgggtg aagtgtggca gtccgggcca gctccagggc ctcagcatct ttgcacagga 2520

cctgcgcctc tgcctggatg aggccctctc ctgggactgt ttcgccctct cgctgctggc 2580

tgtggctctg ggcctgggtg tgcccatgct gcatcacctc tgtggctggg acctctggta 2640

ctgcttccac ctgtgcctgg cctggcttcc ctggcggggg cggcaaagtg ggcgagatga 2700

ggatgccctg ccctacgatg ccttcgtggt cttcgacaaa acgcagagcg cagtggcaga 2760

ctgggtgtac aacgagcttc gggggcagct ggaggagtgc cgtgggcgct gggcactccg 2820

cctgtgcctg gaggaacgcg actggctgcc tggcaaaacc ctctttgaga acctgtgggc 2880

ctcggtctat ggcagccgca agacgctgtt tgtgctggcc cacacggacc gggtcagtgg 2940

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cgtggtgctg gtgatcctga gccctgacgg ccgccgctcc cgctacgtgc ggctgcgcca 3060

gcgcctctgc cgccagagtg tcctcctctg gccccaccag cccagtggtc agcgcagctt 3120

ctgggcccag ctgggcatgg ccctgaccag ggacaaccac cacttctata accggaactt 3180

ctgccaggga cccacggccg aatagccgtg agccggaatc ctgcacggtg ccacctccac 3240

actcacctca cctctgc 3257

<210> 62
<211> 1032
<212> PRT
<213> Homo sapiens

<400> 62

Met Gly Phe Cys Arg Ser Ala Leu His Pro Leu Ser Leu Leu Val Gln
1 5 10 15

Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
20 25 30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
85 90 95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met

```
            100                     105                     110
Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
        115                     120                     125

Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
    130                     135                     140

Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
145                 150                     155                 160

Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
                165                     170                     175

Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
            180                     185                     190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
        195                     200                     205

Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
    210                     215                     220

Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
225                 230                     235                 240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
                245                     250                     255

Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
            260                     265                     270

Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
        275                     280                     285

Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
    290                     295                     300

Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
305                 310                     315                 320

Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
                325                     330                     335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
            340                     345                     350

His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu
        355                     360                     365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
    370                     375                     380

Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
385                 390                     395                 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
                405                     410                     415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu
            420                     425                     430

Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu
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435 440 445
Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
450 455 460

Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
465 470 475 480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
485 490 495

His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
500 505 510

Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
515 520 525

Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
530 535 540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
545 550 555 560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
565 570 575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
580 585 590

Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
595 600 605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
610 615 620

Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
625 630 635 640

His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
645 650 655

Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
660 665 670

Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg
675 680 685

Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
690 695 700

Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
705 710 715 720

Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
725 730 735

Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
740 745 750

Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
755 760 765

Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu

770 775 780
Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
805 810 815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
835 840 845

Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
850 855 860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
865 870 875 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
885 890 895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
900 905 910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
915 920 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
930 935 940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
980 985 990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
995 1000 1005

Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
1010 1015 1020

Asn Phe Cys Gln Gly Pro Thr Ala Glu
1025 1030

<210> 63
<211> 1032
<212> PRT
<213> Homo sapiens

<400> 63

Met Gly Phe Cys Arg Ser Ala Leu His Pro Leu Ser Leu Leu Val Gln
1 5 10 15

Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
20 25 30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
35 40 45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
50 55 60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
65 70 75 80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
85 90 95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
100 105 110

Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
115 120 125

Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
130 135 140

Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
145 150 155 160

Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
180 185 190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
195 200 205

Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
210 215 220

Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
225 230 235 240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
245 250 255

Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
260 265 270

Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
275 280 285

Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
290 295 300

Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
305 310 315 320

Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
325 330 335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
340 345 350

His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu

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        355                 360                 365
Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
    370                 375                 380

Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
385                 390                 395                 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
                405                 410                 415

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ser Glu
            420                 425                 430

Leu Thr Ala Thr Met Gly Glu Ala Asp Gly Gly Glu Lys Val Trp Leu
        435                 440                 445

Gln Pro Gly Asp Leu Ala Pro Ala Pro Val Asp Thr Pro Ser Ser Glu
    450                 455                 460

Asp Phe Arg Pro Asn Cys Ser Thr Leu Asn Phe Thr Leu Asp Leu Ser
465                 470                 475                 480

Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Ala Gln Leu Ser
                485                 490                 495

His Leu Gln Cys Leu Arg Leu Ser His Asn Cys Ile Ser Gln Ala Val
            500                 505                 510

Asn Gly Ser Gln Phe Leu Pro Leu Thr Gly Leu Gln Val Leu Asp Leu
        515                 520                 525

Ser His Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu
    530                 535                 540

Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly
545                 550                 555                 560

Met Gln Gly Val Gly His Asn Phe Ser Phe Val Ala His Leu Arg Thr
                565                 570                 575

Leu Arg His Leu Ser Leu Ala His Asn Asn Ile His Ser Gln Val Ser
            580                 585                 590

Gln Gln Leu Cys Ser Thr Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn
        595                 600                 605

Ala Leu Gly His Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe
    610                 615                 620

Gln Gly Leu Ser Gly Leu Ile Trp Leu Asp Leu Ser Gln Asn Arg Leu
625                 630                 635                 640

His Thr Leu Leu Pro Gln Thr Leu Arg Asn Leu Pro Lys Ser Leu Gln
                645                 650                 655

Val Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Lys Trp Trp Ser
            660                 665                 670

Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Gln
        675                 680                 685

Leu Lys Ala Leu Thr Asn Gly Ser Leu Pro Ala Gly Thr Arg Leu Arg
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690 695 700
Arg Leu Asp Val Ser Cys Asn Ser Ile Ser Phe Val Ala Pro Gly Phe
705 710 715 720

Phe Ser Lys Ala Lys Glu Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala
725 730 735

Leu Lys Thr Val Asp His Ser Trp Phe Gly Pro Leu Ala Ser Ala Leu
740 745 750

Gln Ile Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala
755 760 765

Ala Phe Met Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu
770 775 780

Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Leu Ser
785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp
805 810 815

Asp Cys Phe Ala Leu Ser Leu Leu Ala Val Ala Leu Gly Leu Gly Val
820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His
835 840 845

Leu Cys Leu Ala Trp Leu Pro Trp Arg Gly Arg Gln Ser Gly Arg Asp
850 855 860

Glu Asp Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Thr Gln
865 870 875 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Gly Gln Leu Glu
885 890 895

Glu Cys Arg Gly Arg Trp Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp
900 905 910

Trp Leu Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr
915 920 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
930 935 940

Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Ser Pro Asp Gly Arg
965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
980 985 990

Leu Leu Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln
995 1000 1005

Leu Gly Met Ala Leu Thr Arg Asp Asn His His Phe Tyr Asn Arg
1010 1015 1020

Asn Phe Cys Gln Gly Pro Thr Ala Glu

1025 1030

<210> 64
<211> 333
<212> PRT
<213> Homo sapiens

<400> 64

Met Pro Met Lys Trp Ser Gly Trp Arg Trp Ser Trp Gly Pro Ala Thr
1 5 10 15

His Thr Ala Leu Pro Pro Pro Gln Gly Phe Cys Arg Ser Ala Leu His
20 25 30

Pro Leu Ser Leu Leu Val Gln Ala Ile Met Leu Ala Met Thr Leu Ala
35 40 45

Leu Gly Thr Leu Pro Ala Phe Leu Pro Cys Glu Leu Gln Pro His Gly
50 55 60

Leu Val Asn Cys Asn Trp Leu Phe Leu Lys Ser Val Pro His Phe Ser
65 70 75 80

Met Ala Ala Pro Arg Gly Asn Val Thr Ser Leu Ser Leu Ser Ser Asn
85 90 95

Arg Ile His His Leu His Asp Ser Asp Phe Ala His Leu Pro Ser Leu
100 105 110

Arg His Leu Asn Leu Lys Trp Asn Cys Pro Pro Val Gly Leu Ser Pro
115 120 125

Met His Phe Pro Cys His Met Thr Ile Glu Pro Ser Thr Phe Leu Ala
130 135 140

Val Pro Thr Leu Glu Glu Leu Asn Leu Ser Tyr Asn Asn Ile Met Thr
145 150 155 160

Val Pro Ala Leu Pro Lys Ser Leu Ile Ser Leu Ser Leu Ser His Thr
165 170 175

Asn Ile Leu Met Leu Asp Ser Ala Ser Leu Ala Gly Leu His Ala Leu
180 185 190

Arg Phe Leu Phe Met Asp Gly Asn Cys Tyr Tyr Lys Asn Pro Cys Arg
195 200 205

Gln Ala Leu Glu Val Ala Pro Gly Ala Leu Leu Gly Leu Gly Asn Leu
210 215 220

Thr His Leu Ser Leu Lys Tyr Asn Asn Leu Thr Val Val Pro Arg Asn
225 230 235 240

Leu Pro Ser Ser Leu Glu Tyr Leu Leu Leu Ser Tyr Asn Arg Ile Val
245 250 255

Lys Leu Ala Pro Glu Asp Leu Ala Asn Leu Thr Ala Leu Arg Val Leu
260 265 270

Asp Val Gly Gly Asn Cys Arg Arg Cys Asp His Ala Pro Asn Pro Cys
275 280 285

Met Glu Cys Pro Arg His Phe Pro Gln Leu His Pro Asp Thr Phe Ser
290 295 300

His Leu Ser Arg Leu Glu Gly Leu Val Leu Lys Asp Ser Ser Leu Ser
305 310 315 320

Trp Leu Asn Ala Ser Trp Phe Arg Gly Leu Gly Asn Leu
325 330

<210> 65
<211> 216
<212> PRT
<213> Homo sapiens

<400> 65

Met Leu Tyr Ser Ser Cys Lys Ser Arg Leu Leu Asp Ser Val Glu Gln
1 5 10 15

Asp Phe His Leu Glu Ile Ala Lys Lys Gly Phe Cys Arg Ser Ala Leu
20 25 30

His Pro Leu Ser Leu Leu Val Gln Ala Ile Met Leu Ala Met Thr Leu
35 40 45

Ala Leu Gly Thr Leu Pro Ala Phe Leu Pro Cys Glu Leu Gln Pro His
50 55 60

Gly Leu Val Asn Cys Asn Trp Leu Phe Leu Lys Ser Val Pro His Phe
65 70 75 80

Ser Met Ala Ala Pro Arg Gly Asn Val Thr Ser Leu Ser Leu Ser Ser
85 90 95

Asn Arg Ile His His Leu His Asp Ser Asp Phe Ala His Leu Pro Ser
100 105 110

Leu Arg His Leu Asn Leu Lys Trp Asn Cys Pro Pro Val Gly Leu Ser
115 120 125

Pro Met His Phe Pro Cys His Met Thr Ile Glu Pro Ser Thr Phe Leu
130 135 140

Ala Val Pro Thr Leu Glu Glu Leu Asn Leu Ser Tyr Asn Asn Ile Met
145 150 155 160

Thr Val Pro Ala Leu Pro Lys Ser Leu Ile Ser Leu Ser Leu Ser His
165 170 175

Thr Asn Ile Leu Met Leu Asp Ser Ala Ser Leu Ala Gly Leu His Ala
180 185 190

Leu Arg Phe Leu Phe Met Asp Gly Asn Cys Tyr Tyr Lys Asn Pro Cys
195 200 205

Arg Gln Ala Leu Glu Val Ala Pro
210 215

<210> 66

<211> 117
<212> PRT
<213> Homo sapiens

<400> 66

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Met Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala
1               5                   10                  15

Phe Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp
            20                  25                  30

Leu Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly
        35                  40                  45

Asn Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His
    50                  55                  60

Asp Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys
65                  70                  75                  80

Trp Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His
                85                  90                  95

Met Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu
            100                 105                 110

Leu Asn Leu Ser Tyr
        115
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<210> 67
<211> 1032
<212> PRT
<213> Homo sapiens

<400> 67

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Met Gly Phe Cys Arg Ser Ala Leu His Pro Leu Ser Leu Leu Val Gln
1               5                   10                  15

Ala Ile Met Leu Ala Met Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
            20                  25                  30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu
        35                  40                  45

Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn
    50                  55                  60

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp
65                  70                  75                  80

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp
                85                  90                  95

Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
            100                 105                 110

Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu
        115                 120                 125
```

Asn Leu Ser Tyr Asn Asn Ile Met Thr Val Pro Ala Leu Pro Lys Ser
130 135 140

Leu Ile Ser Leu Ser Leu Ser His Thr Asn Ile Leu Met Leu Asp Ser
145 150 155 160

Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu Glu Val Ala Pro
180 185 190

Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr
195 200 205

Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr
210 215 220

Leu Leu Leu Ser Tyr Asn Arg Ile Val Lys Leu Ala Pro Glu Asp Leu
225 230 235 240

Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
245 250 255

Arg Cys Asp His Ala Pro Asn Pro Cys Met Glu Cys Pro Arg His Phe
260 265 270

Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly
275 280 285

Leu Val Leu Lys Asp Ser Ser Leu Ser Trp Leu Asn Ala Ser Trp Phe
290 295 300

Arg Gly Leu Gly Asn Leu Arg Val Leu Asp Leu Ser Glu Asn Phe Leu
305 310 315 320

Tyr Lys Cys Ile Thr Lys Thr Lys Ala Phe Gln Gly Leu Thr Gln Leu
325 330 335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Gln Lys Arg Val Ser Phe Ala
340 345 350

His Leu Ser Leu Ala Pro Ser Phe Gly Ser Leu Val Ala Leu Lys Glu
355 360 365

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Asp Glu Thr Thr Leu
370 375 380

Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met
385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Gly Ile Phe Arg Ala Phe Pro Gly
405 410 415

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gcaggaggag ctgttgtctg cggatcctca cccagctcca ctgagcaccc ctgcttctaa 1500

gaacttcatg gacaggtgta agaacttcaa gttcaccatg gacctgtctc ggaacaacct 1560

ggtgactatc aagccagaga tgtttgtcaa tctctcacgc ctccagtgtc ttagcctgag 1620

ccacaactcc attgcacagg ctgtcaatgg ctctcagttc ctgccgctga ctaatctgca 1680

ggtgctggac ctgtcccata acaaactgga cttgtaccac tggaaatcgt tcagtgagct 1740

accacagttg caggccctgg acctgagcta caacagccag ccctttagca tgaagggtat 1800

aggccacaat ttcagttttg tgacccatct gtccatgcta cagagcctta gcctggcaca 1860

caatgacatt catacccgtg tgtcctcaca tctcaacagc aactcagtga ggtttcttga 1920

cttcagcggc aacggtatgg gccgcatgtg ggatgagggg ggcctttatc tccatttctt 1980

ccaaggcctg agtggcctgc tgaagctgga cctgtctcaa aataacctgc atatcctccg 2040

gccccagaac cttgacaacc tccccaagag cctgaagctg ctgagcctcc gagacaacta 2100

cctatctttc tttaactgga ccagtctgtc cttcctaccc aacctggaag tcctagacct 2160

ggcaggcaac cagctaaagg ccctgaccaa tggcaccctg cctaatggca ccctcctcca 2220

gaaactcgat gtcagtagca acagtatcgt ctctgtggtc ccagccttct tcgctctggc 2280

ggtcgagctg aaagaggtca acctcagcca caacattctc aagacggtgg atcgctcctg 2340

gtttgggccc attgtgatga acctgacagt tctagacgtg agaagcaacc ctctgcactg 2400

tgcctgtggg gcagccttcg tagacttact gttggaggtg cagaccaagg tgcctggcct 2460

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ctgggtgtat aacgagctgc gggtgcggct ggaggagcgg cgcggtcgcc gagccctacg 2820

cttgtgtctg gaggaccgag attggctgcc tggccagacg ctcttcgaga acctctgggc 2880

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cctcctgcgc accagcttcc tgctggctca gcagcgcctg ttggaagacc gcaaggacgt 3000

ggtggtgttg gtgatcctgc gtccggatgc ccaccgctcc cgctatgtgc gactgcgcca 3060

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ctgggcccag ctgagtacag ccctgactag ggacaaccgc cacttctata accagaactt 3180

ctgccgggga cctacagcag aatagctcag agcaacagct ggaaacagct gcatcttcat 3240

gcctggttcc cgagttgctc tgcctgcctt gctctgtctt actacaccgc tatttggcaa 3300

gtgcgcaata tatgctacca agccaccagg cccacggagc aaaggttggc agtaaagggt 3360

agttttcttc ccatgcatct ttcaggagag tgaagataga caccagaccc acacagaaca 3420

ggactggagt tcattctctg cccctccacc ccactttgcc tgtctctgta t 3471

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<211> 1032
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<213> murine

<400> 72

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Ala Ala Val Leu Ala Glu Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
20 25 30

Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
50 55 60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
65 70 75 80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
85 90 95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
100 105 110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
115 120 125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
130 135 140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145 150 155 160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
180 185 190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
195 200 205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
210 215 220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu
225 230 235 240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
245 250 255

Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
260 265 270

Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
275 280 285

Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
290 295 300

Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
305 310 315 320

Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu
325 330 335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala
340 345 350

Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu
355 360 365

Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu
370 375 380

Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met
385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
405 410 415

Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
420 425 430

Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
435 440 445

Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
450 455 460

Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu

465 470 475 480
Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
485 490 495

Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
500 505 510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
515 520 525

Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
530 535 540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
545 550 555 560

Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Ala His Leu Ser
565 570 575

Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
580 585 590

Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
595 600 605

Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
610 615 620

Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
625 630 635 640

Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
645 650 655

Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
660 665 670

Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
675 680 685

Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
690 695 700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
705 710 715 720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn
725 730 735

Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
740 745 750

Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
755 760 765

Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
770 775 780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
785 790 795 800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser

385 390 395 400
Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
405 410 415

Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
420 425 430

Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
435 440 445

Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
450 455 460

Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu
465 470 475 480

Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
485 490 495

Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
500 505 510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
515 520 525

Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
530 535 540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Gly Tyr Asn Ser Gln Pro Phe
545 550 555 560

Ser Ile Lys Gly Ile Gly His Asn Phe Ser Phe Val Ala His Leu Ser
565 570 575

Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
580 585 590

Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
595 600 605

Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
610 615 620

Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
625 630 635 640

Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
645 650 655

Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
660 665 670

Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
675 680 685

Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
690 695 700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
705 710 715 720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn

725 730 735
Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
740 745 750

Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
755 760 765

Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
770 775 780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
785 790 795 800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser
805 810 815

Trp Asp Cys Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Met Val
820 825 830

Val Pro Ile Leu His His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe
835 840 845

His Leu Cys Leu Ala Trp Leu Pro Leu Leu Ala Arg Ser Arg Arg Ser
850 855 860

Ala Gln Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
865 870 875 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu
885 890 895

Gly Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp
900 905 910

Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr
915 920 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
930 935 940

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His
965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
980 985 990

Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln
995 1000 1005

Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
1010 1015 1020

Asn Phe Cys Arg Gly Pro Thr Ala Glu
1025 1030

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<211> 1032
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Met Val Leu Arg Arg Arg Thr Leu His Pro Leu Ser Leu Leu Val Gln
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Ala Ala Val Leu Ala Glu Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
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Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
        35   40   45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
    50   55   60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
65   70   75   80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
                85   90   95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
            100   105   110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
        115   120   125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
    130   135   140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145   150   155   160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
                165   170   175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
            180   185   190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
        195   200   205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
    210   215   220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu
225   230   235   240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
                245   250   255

Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
            260   265   270

Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
        275   280   285

Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
    290   295   300

Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
305   310   315   320

Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu
325 330 335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala
340 345 350

Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu
355 360 365

Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu
370 375 380

Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met
385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
405 410 415

Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
420 425 430

Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
435 440 445

Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
450 455 460

Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu
465 470 475 480

Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
485 490 495

Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
500 505 510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
515 520 525

Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
530 535 540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
545 550 555 560

Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Thr His Leu Ser
565 570 575

Met Leu Gln Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
580 585 590

Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
595 600 605

Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
610 615 620

Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
625 630 635 640

Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu

645 650 655

Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
660 665 670

Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
675 680 685

Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
690 695 700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
705 710 715 720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn
725 730 735

Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
740 745 750

Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
755 760 765

Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
770 775 780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
785 790 795 800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser
805 810 815

Trp Asp Cys Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Met Val
820 825 830

Val Pro Ile Leu His His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe
835 840 845

His Leu Cys Leu Ala Trp Leu Pro Leu Leu Ala Arg Ser Arg Arg Ser
850 855 860

Ala Gln Thr Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
865 870 875 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu
885 890 895

Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp
900 905 910

Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr
915 920 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
930 935 940

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His
965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val

980 985 990
Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln
995 1000 1005

Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
1010 1015 1020

Asn Phe Cys Arg Gly Pro Thr Ala Glu
1025 1030

<210> 75
<211> 1032
<212> PRT
<213> murine

<400> 75

Met Val Leu Arg Arg Arg Thr Leu His Pro Leu Ser Leu Leu Val Gln
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Ala Ala Val Leu Ala Glu Thr Leu Ala Leu Gly Thr Leu Pro Ala Phe
20 25 30

Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu
35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn
50 55 60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn
65 70 75 80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
85 90 95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met
100 105 110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu
115 120 125

Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser
130 135 140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala
145 150 155 160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro
180 185 190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr
195 200 205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr
210 215 220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu
225 230 235 240

Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg
245 250 255

Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
260 265 270

Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly
275 280 285

Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe
290 295 300

Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu
305 310 315 320

Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu
325 330 335

Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala
340 345 350

Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu
355 360 365

Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu
370 375 380

Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met
385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala
405 410 415

Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr
420 425 430

Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Gln Glu Glu
435 440 445

Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser
450 455 460

Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu
465 470 475 480

Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu
485 490 495

Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala
500 505 510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp
515 520 525

Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu
530 535 540

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe
545 550 555 560

Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Thr His Leu Ser

565 570 575
Met Leu Gln Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val
580 585 590

Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly
595 600 605

Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe
610 615 620

Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn
625 630 635 640

Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu
645 650 655

Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr
660 665 670

Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn
675 680 685

Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu
690 695 700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala
705 710 715 720

Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn
725 730 735

Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn
740 745 750

Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
755 760 765

Ala Ala Phe Val Asp Leu Leu Leu Glu Val Gln Thr Lys Val Pro Gly
770 775 780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg
785 790 795 800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser
805 810 815

Trp Asp Cys Phe Gly Leu Ser Leu Leu Ala Val Ala Val Gly Met Val
820 825 830

Val Pro Ile Leu His His Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe
835 840 845

His Leu Cys Leu Ala Trp Leu Pro Leu Leu Ala Arg Ser Arg Arg Ser
850 855 860

Ala Gln Thr Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln
865 870 875 880

Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu
885 890 895

Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp

900 905 910
Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr
915 920 925

Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser
930 935 940

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu
945 950 955 960

Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Arg Pro Asp Ala His
965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val
980 985 990

Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln
995 1000 1005

Leu Ser Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln
1010 1015 1020

Asn Phe Cys Arg Gly Pro Thr Ala Glu
1025 1030

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<211> 3002
<212> DNA
<213> Homo sapiens

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35 40 45

Ala Thr Thr Thr Leu Asp Leu Ser Tyr Asn Leu Leu Phe Gln Leu Gln
50 55 60

Ser Ser Asp Phe His Ser Val Ser Lys Leu Arg Val Leu Ile Leu Cys
65 70 75 80

His Asn Arg Ile Gln Gln Leu Asp Leu Lys Thr Phe Glu Phe Asn Lys
85 90 95

Glu Leu Arg Tyr Leu Asp Leu Ser Asn Asn Arg Leu Lys Ser Val Thr
100 105 110

Trp Tyr Leu Leu Ala Gly Leu Arg Tyr Leu Asp Leu Ser Phe Asn Asp
115 120 125

Phe Asp Thr Met Pro Ile Cys Glu Glu Ala Gly Asn Met Ser His Leu
130 135 140

Glu Ile Leu Gly Leu Ser Gly Ala Lys Ile Gln Lys Ser Asp Phe Gln
145 150 155 160

Lys Ile Ala His Leu His Leu Asn Thr Val Phe Leu Gly Phe Arg Thr
165 170 175

Leu Pro His Tyr Glu Glu Gly Ser Leu Pro Ile Leu Asn Thr Thr Lys
180 185 190

Leu His Ile Val Leu Pro Met Asp Thr Asn Phe Trp Val Leu Leu Arg
195 200 205

Asp Gly Ile Lys Thr Ser Lys Ile Leu Glu Met Thr Asn Ile Asp Gly
210 215 220

Lys Ser Gln Phe Val Ser Tyr Glu Met Gln Arg Asn Leu Ser Leu Glu
225 230 235 240

Asn Ala Lys Thr Ser Val Leu Leu Leu Asn Lys Val Asp Leu Leu Trp
245 250 255

Asp Asp Leu Phe Leu Ile Leu Gln Phe Val Trp His Thr Ser Val Glu
260 265 270

His Phe Gln Ile Arg Asn Val Thr Phe Gly Gly Lys Ala Tyr Leu Asp
275 280 285

His Asn Ser Phe Asp Tyr Ser Asn Thr Val Met Arg Thr Ile Lys Leu
290 295 300

Glu His Val His Phe Arg Val Phe Tyr Ile Gln Gln Asp Lys Ile Tyr
305 310 315 320

Leu Leu Leu Thr Lys Met Asp Ile Glu Asn Leu Thr Ile Ser Asn Ala
325 330 335

Gln Met Pro His Met Leu Phe Pro Asn Tyr Pro Thr Lys Phe Gln Tyr
340 345 350

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355 360 365

Ile Gln Leu Pro His Leu Lys Thr Leu Ile Leu Asn Gly Asn Lys Leu
370 375 380

Glu Thr Leu Ser Leu Val Ser Cys Phe Ala Asn Asn Thr Pro Leu Glu
385 390 395 400

His Leu Asp Leu Ser Gln Asn Leu Leu Gln His Lys Asn Asp Glu Asn
405 410 415

Cys Ser Trp Pro Glu Thr Val Val Asn Met Asn Leu Ser Tyr Asn Lys
420 425 430

Leu Ser Asp Ser Val Phe Arg Cys Leu Pro Lys Ser Ile Gln Ile Leu
435 440 445

Asp Leu Asn Asn Asn Gln Ile Gln Thr Val Pro Lys Glu Thr Ile His
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Leu Met Ala Leu Arg Glu Leu Asn Ile Ala Phe Asn Phe Leu Thr Asp
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485 490 495

Met Asn Phe Ile Leu Ser Pro Ser Leu Asp Phe Val Gln Ser Cys Gln
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Glu Val Lys Thr Leu Asn Ala Gly Arg Asn Pro Phe Arg Cys Thr Cys
515 520 525

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530 535 540

Val Gly Trp Ser Asp Ser Tyr Thr Cys Glu Tyr Pro Leu Asn Leu Arg
545 550 555 560

Gly Ile Arg Leu Lys Asp Val His Leu His Glu Leu Ser Cys Asn Thr

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Ala Val Ala Phe Cys Cys Leu His Phe Asp Leu Pro Trp Tyr Leu Arg
595 600 605

Met Leu Gly Gln Cys Thr Gln Thr Trp His Arg Val Arg Lys Thr Thr
610 615 620

Gln Glu Gln Leu Lys Arg Asn Val Arg Phe His Ala Phe Ile Ser Tyr
625 630 635 640

Ser Glu His Asp Ser Leu Trp Val Lys Asn Glu Leu Ile Pro Asn Leu
645 650 655

Glu Lys Glu Asp Gly Ser Ile Leu Ile Cys Leu Tyr Glu Ser Tyr Phe
660 665 670

Asp Pro Gly Lys Ser Ile Ser Glu Asn Ile Val Ser Phe Ile Glu Lys
675 680 685

Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro Asn Phe Val Gln Asn Glu
690 695 700

Trp Cys His Tyr Glu Phe Tyr Phe Ala His His Asn Leu Phe His Glu
705 710 715 720

Asn Ser Asp His Ile Ile Leu Ile Leu Leu Glu Pro Ile Pro Phe Tyr
725 730 735

Cys Ile Pro Thr Arg Tyr His Lys Leu Lys Ala Leu Leu Glu Lys Lys
740 745 750

Ala Tyr Leu Glu Trp Pro Lys Asp Arg Arg Lys Cys Gly Leu Phe Trp
755 760 765

Ala Asn Leu Arg Ala Ala Ile Asn Val Asn Val Leu Ala Thr Arg Glu
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Ser Thr Ile Ser Leu Met Arg Thr Asp Cys Leu
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35 40 45

Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
50 55 60

Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
65 70 75 80

Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
85 90 95

Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
100 105 110

Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
115 120 125

Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
130 135 140

Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
145 150 155 160

Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu
165 170 175

Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln
180 185 190

Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu
195 200 205

Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln
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Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys
225 230 235 240

Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Phe Thr Leu
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Asn His Ile Glu Thr Thr Trp Lys Cys Leu Val Arg Val Phe Gln Phe
260 265 270

Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
275 280 285

Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu
290 295 300

Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser
305 310 315 320

Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu
325 330 335

Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro
340 345 350

Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
355 360 365

Ile Phe Glu Lys Cys Ser Thr Leu Val Lys Leu Glu Thr Leu Ile Leu
370 375 380

Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
385 390 395 400

Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
405 410 415

Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
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Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu
435 440 445

Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser
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Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val
465 470 475 480

Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser
485 490 495

Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala
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Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
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Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
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Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys
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Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
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Met Ser Glu Leu Ser Cys Asn Ile Thr Leu Leu Ile Val Thr Ile Gly
580 585 590

Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr
595 600 605

Leu Asp Leu Pro Trp Tyr Leu Arg Met Val Cys Gln Trp Thr Gln Thr

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Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
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Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
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Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
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Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
675 680 685

Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
690 695 700

Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
705 710 715 720

His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
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Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
740 745 750

Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
755 760 765

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Met Thr Lys Asp Lys Glu Pro Ile Val Lys Ser Phe His Phe Val Cys
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Leu Met Ile Ile Ile Val Gly Thr Arg Ile Gln Phe Ser Asp Gly Asn
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Glu Phe Ala Val Asp Lys Ser Lys Arg Gly Leu Ile His Val Pro Lys
35 40 45

Asp Leu Pro Leu Lys Thr Lys Val Leu Asp Met Ser Gln Asn Tyr Ile
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Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
65 70 75 80

Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
85 90 95

Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
100 105 110

Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
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Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
130 135 140

Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
145 150 155 160

Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu
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Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln
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Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu
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Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln
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Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys
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Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
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370 375 380

Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
385 390 395 400

Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
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Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
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Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser
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Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala
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Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
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Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
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Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
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Arg Arg Arg Ala Arg Asn Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
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Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
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Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
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Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
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Ile Asn Cys Ile Glu Lys Ser Tyr Lys Ser Ile Phe Val Leu Ser Pro
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Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
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His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
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Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
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Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
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Ala Glu Leu Gln Val Ser Asp Met Ser Phe Leu Ser Glu Leu Thr Val
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Leu Arg Leu Ser His Asn Arg Ile Gln Leu Leu Asp Leu Ser Val Phe
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Lys Phe Asn Gln Asp Leu Glu Tyr Leu Asp Leu Ser His Asn Gln Leu
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Gln Lys Ile Ser Cys His Pro Ile Val Ser Phe Arg His Leu Asp Leu
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Ser Phe Asn Asp Phe Lys Ala Leu Pro Ile Cys Lys Glu Phe Gly Asn
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Leu Ser Gln Leu Asn Phe Leu Gly Leu Ser Ala Met Lys Leu Gln Lys
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Leu Asp Leu Leu Pro Ile Ala His Leu His Leu Ser Tyr Ile Leu Leu
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Asp Leu Arg Asn Tyr Tyr Ile Lys Glu Asn Glu Thr Glu Ser Leu Gln
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Ile Leu Asn Ala Lys Thr Leu His Leu Val Phe His Pro Thr Ser Leu
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Phe Ala Ile Gln Val Asn Ile Ser Val Asn Thr Leu Gly Cys Leu Gln
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Leu Thr Asn Ile Lys Leu Asn Asp Asp Asn Cys Gln Val Phe Ile Lys
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Leu Trp Pro Lys Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
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Ile Glu Ser Ile Arg Glu Glu Asp Phe Thr Tyr Ser Lys Thr Thr Leu
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Lys Ala Leu Thr Ile Glu His Ile Thr Asn Gln Val Phe Leu Phe Ser
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Gln Thr Ala Leu Tyr Thr Val Phe Ser Glu Met Asn Ile Met Met Leu
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Thr Ile Ser Asp Thr Pro Phe Ile His Met Leu Cys Pro His Ala Pro
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Ser Thr Phe Lys Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
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Gln Lys Asn Gly Leu Lys Asp Leu Phe Lys Val Gly Leu Met Thr Lys
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Asp Met Pro Ser Leu Glu Ile Leu Asp Val Ser Trp Asn Ser Leu Glu
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Ser Gly Arg His Lys Glu Asn Cys Thr Trp Val Glu Ser Ile Val Val
420 425 430

Leu Asn Leu Ser Ser Asn Met Leu Thr Asp Ser Val Phe Arg Cys Leu
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Pro Pro Arg Ile Lys Val Leu Asp Leu His Ser Asn Lys Ile Lys Ser
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Val Pro Lys Gln Val Val Lys Leu Glu Ala Leu Gln Glu Leu Asn Val
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Ala Phe Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ser Phe Ser Ser
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Leu Ser Val Leu Ile Ile Asp His Asn Ser Val Ser His Pro Ser Ala
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Asp Phe Phe Gln Ser Cys Gln Lys Met Arg Ser Ile Lys Ala Gly Asp
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Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Glu Phe Val Lys Asn Ile
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Asp Gln Val Ser Ser Glu Val Leu Glu Gly Trp Pro Asp Ser Tyr Lys
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Cys Asp Tyr Pro Glu Ser Tyr Arg Gly Ser Pro Leu Lys Asp Phe His
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Ala Thr Met Leu Val Leu Ala Val Thr Val Thr Ser Leu Cys Ile Tyr

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Gln Phe His Ala Phe Ile Ser Tyr Ser Glu His Asp Ser Ala Trp Val
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Lys Ser Glu Leu Val Pro Tyr Leu Glu Lys Glu Asp Ile Gln Ile Cys
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Asn Phe Val Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
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His Asn Leu Phe His Glu Gly Ser Asn Asn Leu Ile Leu Ile Leu Leu
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Glu Pro Ile Pro Gln Asn Ser Ile Pro Asn Lys Tyr His Lys Leu Lys
740 745 750

Ala Leu Met Thr Gln Arg Thr Tyr Leu Gln Trp Pro Lys Glu Lys Ser
755 760 765

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Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp
290 295 300

Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu Lys Ser Leu Met Ile
305 310 315 320

Glu His Val Lys Asn Gln Val Phe Leu Phe Ser Lys Glu Ala Leu Tyr
325 330 335

Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu Ser Ile Ser Asp Thr
340 345 350

Pro Phe Ile His Met Val Cys Pro Pro Ser Pro Ser Ser Phe Thr Phe
355 360 365

Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser Val Phe Gln Gly Cys
370 375 380

Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu Gln Arg Asn Gly Leu
385 390 395 400

Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu
405 410 415

Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn Ser His Ala Tyr Asp
420 425 430

Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser
435 440 445

Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu Pro Pro Lys Val Lys
450 455 460

Val Leu Asp Leu His Asn Asn Arg Ile Met Ser Ile Pro Lys Asp Val
465 470 475 480

Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu
485 490 495

Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser Leu Ser Val Leu Val
500 505 510

Ile Asp His Asn Ser Val Ser His Pro Ser Glu Asp Phe Phe Gln Ser
515 520 525

Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn Asn Pro Phe Gln Cys
530 535 540

Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile Gly Trp Val Ala Arg
545 550 555 560

Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu
565 570 575

Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His Met Ser Pro Leu Ser
580 585 590

Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly Ala Thr Met Leu Val

595 600 605
Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr Phe Asp Leu Pro Trp
610 615 620

Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr Arg His Arg Ala Arg
625 630 635 640

His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe
645 650 655

Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val Lys Asn Glu Leu Leu
660 665 670

Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys Leu His Glu Arg Asn
675 680 685

Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Asn Phe Ile Glu
690 695 700

Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro His Phe Ile Gln Ser
705 710 715 720

Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His
725 730 735

Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Leu Gln
740 745 750

Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln
755 760 765

Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe
770 775 780

Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys Leu Ala Leu Val Asn
785 790 795 800

Glu Asp Asp Val Lys Thr
805

<210> 87
<211> 806
<212> PRT
<213> murine

<400> 87

Met Val Lys Ser Leu Trp Asp Ser Leu Cys Asn Met Ser Gln Asp Arg
1 5 10 15

Lys Pro Ile Val Gly Ser Phe His Phe Val Cys Ala Leu Ala Leu Ile
20 25 30

Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu Glu Ser Met Val Asp
35 40 45

Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys Asp Leu Pro Pro Arg
50 55 60

Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile Ser Glu Leu Arg Met
65 70 75 80

Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val Leu Arg Leu Ser His
85 90 95

Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe Leu Phe Asn Gln Asp
100 105 110

Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu Gln Asn Ile Ser Cys
115 120 125

Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu Ser Phe Asn Asp Phe
130 135 140

Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn Leu Thr Lys Leu Thr
145 150 155 160

Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln Leu Asp Leu Leu Pro
165 170 175

Val Ala His Leu His Leu Ser Cys Ile Leu Leu Asp Leu Val Ser Tyr
180 185 190

His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln Ile Pro Asn Thr Thr
195 200 205

Val Leu His Leu Val Phe His Pro Asn Ser Leu Phe Ser Val Gln Val
210 215 220

Asn Met Ser Val Asn Ala Leu Gly His Leu Gln Leu Ser Asn Ile Lys
225 230 235 240

Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr Phe Leu Ser Glu Leu
245 250 255

Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu Gln His Ile Glu Thr
260 265 270

Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe Phe Trp Pro Arg Pro
275 280 285

Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp
290 295 300

Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu Lys Ser Leu Met Ile
305 310 315 320

Glu His Val Lys Asn Gln Val Phe Leu Phe Ser Lys Glu Ala Leu Tyr
325 330 335

Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu Ser Ile Ser Asp Thr
340 345 350

Pro Phe Ile His Met Val Cys Pro Pro Ser Pro Ser Ser Phe Thr Phe
355 360 365

Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser Val Phe Gln Gly Cys
370 375 380

Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu Gln Arg Asn Gly Leu
385 390 395 400

Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu

405 410 415
Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn Ser His Ala Tyr Asp
420 425 430

Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser
435 440 445

Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu Pro Pro Lys Val Lys
450 455 460

Val Leu Asp Leu His Asn Asn Arg Ile Met Ser Ile Pro Lys Asp Val
465 470 475 480

Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu
485 490 495

Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser Leu Ser Val Leu Val
500 505 510

Ile Asp His Asn Ser Val Ser His Pro Ser Glu Asp Phe Phe Gln Ser
515 520 525

Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn Asn Pro Phe Gln Cys
530 535 540

Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile Gly Trp Val Ala Arg
545 550 555 560

Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu
565 570 575

Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His Met Ser Pro Leu Ser
580 585 590

Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly Ala Thr Met Leu Val
595 600 605

Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr Phe Asp Leu Pro Trp
610 615 620

Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr Arg His Arg Ala Arg
625 630 635 640

His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe
645 650 655

Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val Lys Asn Glu Leu Leu
660 665 670

Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys Leu His Glu Arg Asn
675 680 685

Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Asn Phe Ile Glu
690 695 700

Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro His Phe Ile Gln Ser
705 710 715 720

Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His
725 730 735

Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Leu Gln

740 745 750
Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln
755 760 765

Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe
770 775 780

Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys Leu Ala Leu Val Asn
785 790 795 800

Glu Asp Asp Val Lys Thr
805

<210> 88
<211> 806
<212> PRT
<213> murine

<400> 88

Met Val Lys Ser Leu Trp Asp Ser Leu Cys Asn Met Ser Gln Asp Arg
1 5 10 15

Lys Pro Ile Val Gly Ser Phe His Phe Val Cys Ala Leu Ala Leu Ile
20 25 30

Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu Glu Ser Met Val Asp
35 40 45

Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys Asp Leu Pro Pro Arg
50 55 60

Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile Ser Glu Leu Arg Met
65 70 75 80

Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val Leu Arg Leu Ser His
85 90 95

Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe Leu Phe Asn Gln Asp
100 105 110

Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu Gln Asn Ile Ser Cys
115 120 125

Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu Ser Phe Asn Asp Phe
130 135 140

Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn Leu Thr Lys Leu Thr
145 150 155 160

Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln Leu Asp Leu Leu Pro
165 170 175

Val Ala His Leu His Leu Ser Cys Ile Leu Leu Asp Leu Val Ser His
180 185 190

His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln Ile Pro Asn Thr Thr
195 200 205

Val Leu His Leu Val Phe His Pro Asn Ser Leu Phe Ser Val Gln Val
210 215 220

Asn Met Ser Val Asn Ala Leu Gly His Leu Gln Leu Ser Asn Ile Lys
225 230 235 240

Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr Phe Leu Ser Glu Leu
245 250 255

Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu Gln His Ile Glu Thr
260 265 270

Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe Phe Trp Pro Arg Pro
275 280 285

Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile Thr Glu Arg Ile Asp
290 295 300

Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu Lys Ser Leu Met Ile
305 310 315 320

Glu His Val Lys Asn Gln Val Phe Leu Phe Ser Lys Glu Ala Leu Tyr
325 330 335

Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu Ser Ile Ser Asp Thr
340 345 350

Pro Phe Ile His Met Val Cys Pro Pro Ser Pro Ser Ser Phe Thr Phe
355 360 365

Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser Val Phe Gln Gly Cys
370 375 380

Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu Gln Arg Asn Gly Leu
385 390 395 400

Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys Asn Met Ser Ser Leu
405 410 415

Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn Ser His Ala Tyr Asp
420 425 430

Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val Leu Asn Leu Ser Ser
435 440 445

Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu Pro Pro Lys Val Lys
450 455 460

Val Leu Asp Leu His Asn Asn Arg Ile Met Ser Ile Pro Lys Asp Val
465 470 475 480

Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val Ala Ser Asn Ser Leu
485 490 495

Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser Leu Ser Val Leu Val
500 505 510

Ile Asp His Asn Ser Val Ser His Pro Ser Glu Asp Phe Phe Gln Ser
515 520 525

Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn Asn Pro Phe Gln Cys
530 535 540

Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile Gly Trp Val Ala Arg

545 550 555 560
Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg Cys Asp Tyr Pro Glu
565 570 575

Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His Met Ser Pro Leu Ser
580 585 590

Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly Ala Thr Met Leu Val
595 600 605

Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr Phe Asp Leu Pro Trp
610 615 620

Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr Arg His Arg Ala Arg
625 630 635 640

His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu Gln Phe His Ala Phe
645 650 655

Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val Lys Asn Glu Leu Leu
660 665 670

Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys Leu His Glu Arg Asn
675 680 685

Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile Ile Asn Phe Ile Glu
690 695 700

Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro His Phe Ile Gln Ser
705 710 715 720

Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His His Asn Leu Phe His
725 730 735

Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu Glu Pro Ile Leu Gln
740 745 750

Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg Ala Leu Met Ala Gln
755 760 765

Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly Lys Arg Gly Leu Phe
770 775 780

Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys Leu Ala Leu Val Asn
785 790 795 800

Glu Asp Asp Val Lys Thr
805

<210> 89
<211> 795
<212> PRT
<213> murine

<400> 89

Met Ser Gln Asp Arg Lys Pro Ile Val Gly Ser Phe His Phe Val Cys
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Ala Leu Ala Leu Ile Val Gly Ser Met Thr Pro Phe Ser Asn Glu Leu
20 25 30

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Glu Ser Met Val Asp Tyr Ser Asn Arg Asn Leu Thr His Val Pro Lys
        35                  40                  45

Asp Leu Pro Pro Arg Thr Lys Ala Leu Ser Leu Ser Gln Asn Ser Ile
    50                  55                  60

Ser Glu Leu Arg Met Pro Asp Ile Ser Phe Leu Ser Glu Leu Arg Val
65                  70                  75                  80

Leu Arg Leu Ser His Asn Arg Ile Arg Ser Leu Asp Phe His Val Phe
                85                  90                  95

Leu Phe Asn Gln Asp Leu Glu Tyr Leu Asp Val Ser His Asn Arg Leu
            100                 105                 110

Gln Asn Ile Ser Cys Cys Pro Met Ala Ser Leu Arg His Leu Asp Leu
        115                 120                 125

Ser Phe Asn Asp Phe Asp Val Leu Pro Val Cys Lys Glu Phe Gly Asn
    130                 135                 140

Leu Thr Lys Leu Thr Phe Leu Gly Leu Ser Ala Ala Lys Phe Arg Gln
145                 150                 155                 160

Leu Asp Leu Leu Pro Val Ala His Leu His Leu Ser Cys Ile Leu Leu
                165                 170                 175

Asp Leu Val Ser Tyr His Ile Lys Gly Gly Glu Thr Glu Ser Leu Gln
            180                 185                 190

Ile Pro Asn Thr Thr Val Leu His Leu Val Phe His Pro Asn Ser Leu
        195                 200                 205

Phe Ser Val Gln Val Asn Met Ser Val Asn Ala Leu Gly His Leu Gln
    210                 215                 220

Leu Ser Asn Ile Lys Leu Asn Asp Glu Asn Cys Gln Arg Leu Met Thr
225                 230                 235                 240

Phe Leu Ser Glu Leu Thr Arg Gly Pro Thr Leu Leu Asn Val Thr Leu
                245                 250                 255

Gln His Ile Glu Thr Thr Trp Lys Cys Ser Val Lys Leu Phe Gln Phe
            260                 265                 270

Phe Trp Pro Arg Pro Val Glu Tyr Leu Asn Ile Tyr Asn Leu Thr Ile
        275                 280                 285

Thr Glu Arg Ile Asp Arg Glu Glu Phe Thr Tyr Ser Glu Thr Ala Leu
    290                 295                 300

Lys Ser Leu Met Ile Glu His Val Lys Asn Gln Val Phe Leu Phe Ser
305                 310                 315                 320

Lys Glu Ala Leu Tyr Ser Val Phe Ala Glu Met Asn Ile Lys Met Leu
                325                 330                 335

Ser Ile Ser Asp Thr Pro Phe Ile His Met Val Cys Pro Pro Ser Pro
            340                 345                 350

Ser Ser Phe Thr Phe Leu Asn Phe Thr Gln Asn Val Phe Thr Asp Ser
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355 360 365
Val Phe Gln Gly Cys Ser Thr Leu Lys Arg Leu Gln Thr Leu Ile Leu
370 375 380

Gln Arg Asn Gly Leu Lys Asn Phe Phe Lys Val Ala Leu Met Thr Lys
385 390 395 400

Asn Met Ser Ser Leu Glu Thr Leu Asp Val Ser Leu Asn Ser Leu Asn
405 410 415

Ser His Ala Tyr Asp Arg Thr Cys Ala Trp Ala Glu Ser Ile Leu Val
420 425 430

Leu Asn Leu Ser Ser Asn Met Leu Thr Gly Ser Val Phe Arg Cys Leu
435 440 445

Pro Pro Lys Val Lys Val Leu Asp Leu His Asn Asn Arg Ile Met Ser
450 455 460

Ile Pro Lys Asp Val Thr His Leu Gln Ala Leu Gln Glu Leu Asn Val
465 470 475 480

Ala Ser Asn Ser Leu Thr Asp Leu Pro Gly Cys Gly Ala Phe Ser Ser
485 490 495

Leu Ser Val Leu Val Ile Asp His Asn Ser Val Ser His Pro Ser Glu
500 505 510

Asp Phe Phe Gln Ser Cys Gln Asn Ile Arg Ser Leu Thr Ala Gly Asn
515 520 525

Asn Pro Phe Gln Cys Thr Cys Glu Leu Arg Asp Phe Val Lys Asn Ile
530 535 540

Gly Trp Val Ala Arg Glu Val Val Glu Gly Trp Pro Asp Ser Tyr Arg
545 550 555 560

Cys Asp Tyr Pro Glu Ser Ser Lys Gly Thr Ala Leu Arg Asp Phe His
565 570 575

Met Ser Pro Leu Ser Cys Asp Thr Val Leu Leu Thr Val Thr Ile Gly
580 585 590

Ala Thr Met Leu Val Leu Ala Val Thr Gly Ala Phe Leu Cys Leu Tyr
595 600 605

Phe Asp Leu Pro Trp Tyr Val Arg Met Leu Cys Gln Trp Thr Gln Thr
610 615 620

Arg His Arg Ala Arg His Ile Pro Leu Glu Glu Leu Gln Arg Asn Leu
625 630 635 640

Gln Phe His Ala Phe Val Ser Tyr Ser Glu His Asp Ser Ala Trp Val
645 650 655

Lys Asn Glu Leu Leu Pro Asn Leu Glu Lys Asp Asp Ile Arg Val Cys
660 665 670

Leu His Glu Arg Asn Phe Val Pro Gly Lys Ser Ile Val Glu Asn Ile
675 680 685

Ile Asn Phe Ile Glu Lys Ser Tyr Lys Ala Ile Phe Val Leu Ser Pro

690 695 700
His Phe Ile Gln Ser Glu Trp Cys His Tyr Glu Leu Tyr Phe Ala His
705 710 715 720

His Asn Leu Phe His Glu Gly Ser Asp Asn Leu Ile Leu Ile Leu Leu
725 730 735

Glu Pro Ile Leu Gln Asn Asn Ile Pro Ser Arg Tyr His Lys Leu Arg
740 745 750

Ala Leu Met Ala Gln Arg Thr Tyr Leu Glu Trp Pro Thr Glu Lys Gly
755 760 765

Lys Arg Gly Leu Phe Trp Ala Asn Leu Arg Ala Ser Phe Ile Met Lys
770 775 780

Leu Ala Leu Val Asn Glu Asp Asp Val Lys Thr
785 790 795

<210> 90
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> consensus p50 subunit

<220>
<221> misc_feature
<222> (7)..(7)
<223> N = c or t

<400> 90
ggggatnccc 10

<210> 91
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> consensus p65 subunit

<220>
<221> misc_feature
<222> (4)..(4)
<223> N = a or g

<220>
<221> misc_feature
<222> (5)..(5)
<223> N = a, c, g, or t

<400> 91
gggnntttcc 10

<210> 92

<211> 22
<212> DNA
<213> artificial sequence

<220>

<223> consensus subunit

<400> 92
agttgagggg actttcccag gc 22

<210> 93
<211> 27
<212> DNA
<213> artificial sequence

<220>

<223> CREB binding site

<400> 93
agagattgcc tgacgtcaga gagctag 27

<210> 94
<211> 21
<212> DNA
<213> artificial sequence

<220>

<223> AP-1 binding site

<400> 94
cgcttgatga gtcagccgga a 21

<210> 95
<211> 15
<212> DNA
<213> artificial sequence

<220>

<223> AP-1 binding site

<400> 95
cgcatgagtc agaca 15

<210> 96
<211> 19
<212> DNA
<213> artificial sequence

<220>

<223> ISRE

<400> 96

tgcagaagtg aaactgagg 19

<210> 97
<211> 11
<212> DNA
<213> artificial sequence

<220>

<223> ISRE

<400> 97
agaacgaaac a 11

<210> 98
<211> 15
<212> DNA
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<220>

<223> ISRE

<400> 98
gagaagtgaa agtgg 15

<210> 99
<211> 18
<212> DNA
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<220>

<223> ISRE

<400> 99
taagaacatg aaactgaa 18

<210> 100
<211> 15
<212> DNA
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<220>

<223> ISRE

<400> 100
atgaaactga aagta 15

<210> 101
<211> 16
<212> DNA
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<220>

<223> ISRE

<400> 101
tgaaaaccga aagcgc 16

<210> 102
<211> 13
<212> DNA
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<220>

<223> ISRE

<400> 102
agaaatggaa agt 13

<210> 103
<211> 9
<212> DNA
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<220>

<223> SRE

<400> 103
tcaccccac 9

<210> 104
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> SRE

<400> 104
ctcaccccac 10

<210> 105
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> SRE

<400> 105
gccaccctac 10

<210> 106
<211> 17
<212> DNA
<213> artificial sequence

<220>
<223> NFAT

<400> 106
tatgaaacag tttttcc 17

<210> 107
<211> 9
<212> DNA
<213> artificial sequence

<220>

<223> NFAT

<400> 107
aggaaactc 9

<210> 108
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> NFAT

<220>
<221> misc_feature
<222> (2)..(2)
<223> N = a or g

<220>
<221> misc_feature
<222> (5)..(5)
<223> N = a or g

<400> 108
anganattcc 10

<210> 109
<211> 16
<212> DNA
<213> artificial sequence

<220>

<223> NFAT

<400> 109
ccagttgagc cagaga 16

<210> 110
<211> 30
<212> DNA
<213> artificial sequence

<220>

<223> GAS

<400> 110
ctttcagttt catattactc taaatccatt 30

<210> 111
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<220>
<221> misc_feature
<222> (1)..(3)
<223> N = a or g

<220>
<221> misc_feature
<222> (5)..(6)
<223> N = a or t

<220>
<221> misc_feature
<222> (8)..(10)
<223> N = c or t

<400> 111
nnncnngnnn 10

<210> 112
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 112
aggcatgcct 10

<210> 113
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 113
gggcttgccc 10

<210> 114

<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 114
gggcttgctt 10

<210> 115
<211> 13
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 115
gcctggactt gcc 13

<210> 116
<211> 20
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 116
ggacatgccc gggcatgtcc 20

<210> 117
<211> 23
<212> DNA
<213> artificial sequence

<220>

<223> p53 consensus site

<400> 117
gtagcattag cccagacatg tcc 23

<210> 118
<211> 36
<212> DNA
<213> artificial sequence

<220>

<223> TARE

<400> 118
gaggtatgca gacaagagtc agagtttccc cttgaa 36

<210> 119
<211> 10
<212> DNA
<213> artificial sequence

<220>

<223> SRF

<220>
<221> misc_feature
<222> (3)..(8)
<223> N = a or t

<400> 119
ccnnnnnngg 10

<210> 120
<211> 11
<212> DNA
<213> artificial sequence

<220>

<223> SRF

<400> 120
ccaaataagg c 11

<210> 121
<211> 670
<212> DNA
<213> Homo sapiens

<400> 121
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aattatattc atattattaa tgtgtatcta tatagatttt tattttgcat atgtactttg 120

atacaaaatt tacatgaaca aattacacta aaagttattc cacaaatata cttatcaaat 180

taagttaaat gtcaatagct tttaaactta aattttagtt taacttttct gtcattcttt 240

actttgaata aaaagagcaa actttgtagt ttttatctgt gaagtagagg tatacgtaat 300

atacataaat agatatgcca aatctgtgtt attaaaattt catgaagatt tcaattagaa 360

aaaaatacca taaaaggctt tgagtgcagg tgaaaaatag gcaatgatga aaaaaaatga 420

aaaacttttt aaacacatgt agagagtgcg taaagaaagc aaaaacagag atagaaagta 480

caactaggga atttagaaaa tggaaattag tatgttcact atttaagacc tatgcacaga 540

gcaaagtctt cagaaaacct agaggccgaa gttcaaggtt atccatctca agtagcctag 600

caatatttgc aacatcccaa tggccctgtc cttttcttta ctgatggccg tgctggtgct 660

cagctacaaa 670

<210> 122
<211> 207
<212> DNA
<213> Homo sapiens

<400> 122
aggttctctg aaggccttgc ttcctgcaga tgccttaaat agggaacata ctgatttcca 60

ctttcttaat gcttctggac catttccatt tctgtttttg ctttccttct taactcttta 120

catgagttta gagccgtgtt tctcaaatga tgggctagca cgcgtaagag ctcggtacct 180

atcgatagag aaatgttctg gcacctg 207

<210> 123
<211> 161
<212> DNA
<213> Homo sapiens

<400> 123
aggttctctg aaggctttgc ttcctgcaga tgccttaaat agggaacata ctgatttcca 60

ctttcttaat gcttctggac cactttccat ttctgttttt gctttccttc ttgaactctt 120

tacatgagtt tagagccgtg tttctcaacc attttgtttt t 161

<210> 124
<211> 300
<212> DNA
<213> Homo sapiens

<400> 124
ttctcaggtc gtttgctttc ctttgctttc tcccaagtct tgttttacaa tttgctttag 60

tcattcactg aaactttaaa aaacattaga aaacctcaca gtttgtaaat ctttttccct 120

attatatata tcataagata ggagcttaaa taaagagttt tagaaactac taaaatgtaa 180

atgacatagg aaaactgaaa gggagaagtg aaagtgggaa attcctctga atagagagag 240

gaccatctca tataaatagg ccatacccac ggagaaagga cattctaact gcaacctttc 300

<210> 125
<211> 401
<212> DNA
<213> Homo sapiens

<400> 125
gatctgtaat gaataagcag gaactttgaa gactcagtga ctcagtgagt aataaagact 60

cagtgacttc tgatcctgtc ctaactgcca ctccttgttg tcccaagaaa gcggcttcct 120

gctctctgag gaggacccct tccctggaag gtaaaactaa ggatgtcagc agagaaattt 180

ttccaccatt ggtgcttggt caaagaggaa actgatgagc tcactctaga tgagagagca 240

gtgagggaga gacagagact cgaatttccg gagctatttc agttttcttt tccgttttgt 300

gcaatttcac ttatgatacc ggccaatgct tggttgctat tttggaaact ccccttaggg 360
gatgcccctc aactggccct ataaagggcc agcctgagct g 401

<210> 126
<211> 781
<212> DNA
<213> Homo sapiens

<400> 126
ggttgtctgt atgcctccct gagggtattt cactttctgc tcccatccgc ccctatgagc 60

gagtacctat gagcacagga tgtgcacata tttgagtctt attagtggta cacgcagttt 120

tatcatctcc ccaggtctgt gtctgtatga aatgtgcatg ggtgtgtgtg tgcacgcgtg 180

tgttcccact cggggaatgt ggggagaggt gcatggagcc aagatgggtg gtaaatagta 240

tgtttctgaa attaaaggac taatgtggag gaaggcgccc cagatgtact aaaccctttg 300

ccttcatctc atcctctctg acttgggaag aaccaggatt ttgtttttaa gcccttgggc 360

atacagttgt tccatcccga catgaactca gcctcccgtc tgaccgcccc ttggccttcc 420

ttcttcctcg atctgtggaa cccagggaat ctgcctagtg ctgtctccaa gcaccttggc 480

catgatgtaa acccagagaa attagcatct ccatctcctt ccttattccc cacccaaaag 540

tcatttcctc ttagttcatt acctgggatt ttgatgtcta tgttccctcc tcgttattga 600

tacacacaca gagagagaca aacaaaaaag gaacttcttg aaattccccc agaaggtttt 660

gagagttgtt ttcaatgttg caacaagtca gtttctagtt taagtttcca tcagaaagga 720

gtagagtata taagttccag taccagcaac agcagcagaa gaaacaacat ctgtttcagg 780

g 781

<210> 127
<211> 277
<212> DNA
<213> Homo sapiens

<400> 127
gcatctccat ctccttcctt attccccacc caaaagtcat ttcctcttag ttcattacct 60

gggattttga tgtctatgtt ccctcctcgt tattgataca cacacagaga gagacaaaca 120

aaaaaggaac ttcttgaaat tcccccagaa ggttttgaga gttgttttca atgttgcaac 180

aagtcagttt ctagtttaag tttccatcag aaaggagtag agtatataag ttccagtacc 240

agcaacagca gcagaagaaa caacatctgt ttcaggg 277

<210> 128
<211> 305
<212> DNA
<213> Homo sapiens

<400> 128

caagacatgc caagtgctga gtcactaata aagaaaaaag aagtaaagga agagtggttc 60
tgcttcttag cgctagcctc aatgacgacc taagctgcac ttttccccct agttgtgtct 120

tgcgatgcta aaggacgtca ttgcacaatc ttaataaggt ttccaatcag ccccacccgc 180

tctggcccca ccctcaccct ccaacaaaga tttatcaaat gtgggatttt cccatgagtc 240

tcaatattag agtctcaacc cccaataaat ataggactgg agatgtctct gaggctcatt 300

ctgcc 305

<210> 129
<211> 1181
<212> DNA
<213> Homo sapiens

<400> 129
cctgcaagag acaccatcct gaggggaaga gggcttctga accagcttga cccaataaga 60

aattcttggg tgccgacggg gacagcagat tcagagccta gagccgtgcc tgcgtccgta 120

gtttccttct agcttctttt tgatttcaaa tcaagactta cagggagagg gagcgataaa 180

cacaaactct gcaagatgcc acaaggtcct cctttgacat ccccaacaaa gaaggtgagt 240

agtaatctcc ccctttctgc cctgaaccaa gtggcttcag taagtttcag ggctccagga 300

gacctgggca tgcaggtgcc gatgaaacag tggtgaagag actcagtggc agtggcagtg 360

gggagagcac tcgcagcaca ggcaaacctc tggcacaaga gcaaagtcct cactggagga 420

ttcccaaggg tcacttggga gagggcaggc agcagccaac ctcctctaag tgggctgaag 480

caggtgaaga aatggcagaa gacgcggtgg tggcaaaaag gagtcacaca ctccacctgg 540

agacgccttg aagtaactgc acgaaatttg agggtggcca ggcagttcta caacagccgc 600

ctcacaggga gagccagaac acagcaagaa ctcagatgac tggtagtatt accttcttca 660

taatcccagg cttgggggc tgcgatggag tcagaggaaa ctcagttcag aacatctttg 720

gtttttacaa tacaaattaa ctggaacgct aaattctagc ctgttaatct ggtcactgaa 780

aaaaaaaaaa tttttttttt ttcaaaaaac atagctttag cttatttttt ttttctcttt 840

gtaaaacttc gtgcatgact tcagctttac tcttgtcaag acatgccaag tgctgagtca 900

ctaataaaga aaaaagaagt aaaggaagag tggttctgct tcttagcgct agcctcaatg 960

acgacctaag ctgcactttt ccccctagtt gtgtcttgcg atgctaaagg acgtcattgc 1020

acaatcttaa taaggtttcc aatcagcccc acccgctctg gccccaccct caccctccaa 1080

caaagattta tcaaatgtgg gattttccca tgagtctcaa tattagagtc tcaaccccca 1140

ataaatatag gactggagat gtctctgagg ctcattctgc c 1181

<210> 130
<211> 778
<212> DNA

<213> Homo sapiens
<400> 130
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ccaaactctt taaggacaag tacctagtct tatctatttc tagatccccc acattactca 120

gaaagttact ccataaatgt ttgtggaact gatttctatg tgaagacatg tgccccttca 180

ctctgttaac tagcattaga aaaacaaatc ttttgaaaag ttgtagtatg cccctaagag 240

cagtaacagt tcctagaaac tctctaaaat gcttagaaaa agatttattt taaattacct 300

ccccaataaa atgattggct ggcttatctt caccatcatg atagcatctg taattaactg 360

aaaaaaaata attatgccat taaaagaaaa tcatccatga tcttgttcta acacctgcca 420

ctctagtact atatctgtca catggtctat gataaagtta tctagaaata aaaaagcata 480

caattgataa ttcaccaaat tgtggagctt cagtatttta aatgtatatt aaaattaaat 540

tattttaaag atcaaagaaa actttcgtca tactccgtat ttgataagga acaaatagga 600

agtgtgatga ctcaggtttg ccctgagggg atgggccatc agttgcaaat cgtggaattt 660

cctctgacat aatgaaaaga tgagggtgca taagttctct agtagggtga tgatataaaa 720

agccaccgga gcactccata aggcacaaac tttcagagac agcagagcac acaagctt 778

<210> 131
<211> 207
<212> DNA
<213> Homo sapiens

<400> 131
actccgtatt tgataaggaa caaataggaa gtgtgatgac tcaggtttgc cctgagggga 60

tgggccatca gttgcaaatc gtggaatttc ctctgacata atgaaaagat gagggtgcat 120

aagttctcta gtagggtgat gatataaaaa gccaccggag cactccataa ggcacaaact 180

ttcagagaca gcagagcaca caagctt 207

<210> 132
<211> 645
<212> DNA
<213> Homo sapiens

<400> 132
gggggtgatt tcactccccg gggctgtccc aggcttgtcc ctgctacccg cacccagcct 60

ttcctgaggc ctcaagcctg ccaccaagcc cccagctcct tctccccgca gggcccaaac 120

acaggcctca ggactcaaca cagcttttcc ctccaacccc gttttctctc cctcaacgga 180

ctcagctttc tgaagcccct cccagttcta gttctatctt tttcctgcat cctgtctgga 240

agttagaagg aaacagacca cagacctggt ccccaaaaga aatggaggca ataggttttg 300

aggggcatgg ggacggggtt cagcctccag ggtcctacac acaaatcagt cagtggccca 360

gaagaccccc ctcggaatcg gagcagggag gatggggagt gtgaggggta tccttgatgc 420
ttgtgtgtcc ccaactttcc aaatccccgc ccccgcgatg gagaagaaac cgagacagaa 480

ggtgcagggc ccactaccgc ttcctccaga tgagctcatg ggtttctcca ccaaggaagt 540

tttccgctgg ttgaatgatt ctttccccgc cctcctctcg ccccagggac atataaaggc 600

agttgttggc acacccagcc agcagacgct ccctcagcaa ggaca 645

<210> 133
<211> 457
<212> DNA
<213> Homo sapiens

<400> 133
gcctgtactc agccaagggt gcagagatgt tatatatgat tgctcttcag ggaaccgggc 60

ctccagctca caccccagct gctcaaccac ctcctctctg aattgactgt cccttctttg 120

gaactctagg cctgacccca ctccctggcc ctcccagccc acgattcccc tgacccgact 180

ccctttccca gaactcagtc gcctgaaccc ccagcctgtg gttctctcct aggcctcagc 240

ctttcctgcc tttgactgaa acagcagtat cttctaagcc ctgggggctt ccccgggccc 300

cagccccgac ctagaacccg cccgctgcct gccacgctgc cactgccgct tcctctataa 360

agggacctga gcgtccgggc ccaggggctc cgcacagcag gtgaggctct cctgccccat 420

ctccttgggc tgcccgtgct tcgtgctttg gactacc 457

<210> 134
<211> 973
<212> DNA
<213> Homo sapiens

<400> 134
gcagcaaatc agaatggcag tttgattcat ggtgctgaga ctggaggttc ctctgctgta 60

ggctcagaat atgtctaagc aattgaggaa tgtctcagaa aacgtggggc tagtgtgcca 120

tatttatctg caaagccatt ttccctccct aattctgatt ggataagggc attacagttg 180

acttagcaaa acctgctggc tgttcctggg gaagtcccat gttgcagact cgaaggtatt 240

atttattgta gcctccaagt tacggaattt ccctctgctc ctcttttttt ggtaatagtg 300

aattaggttt cactttccaa aacatgaact gtttcttgaa aaaaagaact tcattgcata 360

tagaaaaaaa caaaggttgc aatccattct aactataatg ctttttctca acacttaaac 420

ttttacagtt actttcagag gttatttttc aaaatatccc cagtaataga aatttttcat 480

cctttatagg taaacctaat tttttggtaa cagcaagttg tgcctgatta ttagaacagt 540

gatttacctg gacagtcctc cttgatcaaa tactataaag taataggact ggcctgcttt 600

gacagggtca aagatctgga actggcaagt tttaaataat tcaataaatg ctttgatcat 660

tcataacacc attagattaa gtaaatagcc tccaacataa ctattttgag ggaaaacatt 720

gctcatttgg gtatctgatt tgtggtgtgt taaaacaagt ttcacgtctt atagcagtcc 780

ctgaatgaaa acatcataag atggtatcta gaatggtgtg agaaaaggat tcatagctat 840

cctagggtta ttgtaaaaaa caaagggtgc tttttgagga aatgaattta aaagcggggg 900

ggcacgcata gagacagacc ttgggaaagt agcttgagac agaagggaaa caggttgatt 960

tacgatgggg ttc 973

<210> 135
<211> 333
<212> DNA
<213> Homo sapiens

<400> 135
gctaccttaa gaaggctggt taccatctgg gttttcacag tgctttcaca ttcttatcac 60

tttcaacact actgcaaata ggaagggaca gtaacattta gaagagaaca aaacagaaac 120

tcttggaagc aggaaaggtg catgactcaa agagggaaat tcctgtgcca taaaaggatt 180

gctggtgtat aaaatgctct atatatgcca attatcaatt tcctttcatg ttcagcattt 240

ctactccttc caagaagagc agcaaagctg aagttagcag cagcagcacc agcagcaaca 300

gcaaaaaaca aacatgagtg tgaagggcat ggc 333

<210> 136
<211> 1048
<212> DNA
<213> Homo sapiens

<400> 136
ggtgaccaag aatgtgagca agcccaggca cagccactgt gggcgcctga ccaaacagca 60

ctaaatttgt gtgggacatg atcccagagg tgtgtggctt cacccctcaa cgagtggcgt 120

ggcatggagt tactgaatct ccaaggtcaa acaggccctc aaattcatca agaaaagggt 180

agggacaaac atctgtacca agagaaggca ggaggagctg agcaacgtcc tgctgccatg 240

aggaaagcag ctgccaagaa ggactgagcc cctgccatct gcctataatg aaagctttgc 300

aaaataaaat aaatataaaa taaagtaata aaattaaatt aaatttaaaa ataaaataaa 360

gcaaaacaaa ataaaatata taaagtaaaa attgttaaaa tgcaaaacaa tatggacata 420

aatacagaaa cacagggaaa cttctttagg cactcattta caggtaaaaa tatgaaattg 480

aataaaggtc atctggtgtc aaataatata ggccttatct attataagag tttggactga 540

aaagcaaaag tgagataaca aaaaaaagct tttcagaata ttattttgta tagatatgtg 600

aaggatgaag ggtgggtgaa aggaccaaaa acagaaacac agtcttcctg aatgaatgac 660

aatcagaatt ccgctgccca aagtagtccg acaattaaat ggatttctag gaaaagctac 720

cttaagaagg ctggttacca tctgggtttt cacagtgctt tcacattctt atcactttca 780

acactactgc aaataggaag ggacagtaac atttagaaga gaacaaaaca gaaactcttg 840

gaagcaggaa aggtgcatga ctcaaagagg gaaattcctg tgccataaaa ggattgctgg 900

tgtataaaat gctctatata tgccaattat caatttcctt tcatgttcag catttctact 960

ccttccaaga agagcagcaa agctgaagtt agcagcagca gcaccagcag caacagcaaa 1020

aaacaaacat gagtgtgaag ggcatggc 1048

<210> 137
<211> 504
<212> DNA
<213> Homo sapiens

<400> 137
agggggcccc gcagcagccc cttggcttcc cttctccctt gcctcccctc cggggctccg 60

gttcagaggc actctgggcg cctgctacag cttccaaact gcgccgcttc cttcttcggc 120

agaaaaggac tttcagatgc ggcggcggcg gcggcggcga ctcaggacag cgccccctcc 180

cctaacggcc gcctctccct ctccccctcg cccgccccgg ctcccccacc tctgggaagg 240

cgctgggggt gtggccaggg accggtataa agtccggggg agccggtccc gggcagccgc 300

tcagccccct gcccctcgcc gcccgccgcc tgcctgggcc gggccgagga tgcggcgcag 360

cgcctcggcg gccaggcttg ctccctccgg cacgcctgct aacttccccc gctacgtccc 420

cgttcgcccg ccgggccgcc ccgtctcccc gcgccctccg ggtcgggtcc tccaggagcg 480

ccaggcgctg ccgccgtgtg ccct 504

<210> 138
<211> 1042
<212> DNA
<213> Homo sapiens

<400> 138
gatcacaaca gctctacaaa tacacaatga ttacaaggaa tggtgcccca ctggagttgt 60

tcaacgcaaa acttgcacat tgcaagtggc aatctcccag gcctgcctcc ctccacgagt 120

gggtctgaat gggcctgaga ggcaaacatc caagaaggag gaagaggctc ggcggcacct 180

ccctccccgg gagttctgct gattccatct tggggaagca gggtggacca gggcccaaat 240

gcgccctggg gagattgcgg gggcgggaga ggttgcaagg ggcaagtggc aagagcctgt 300

taacgtctta gggcctccag gcctttctgt gcccctagct gtgcctgtac gctttacccc 360

acctcaggag gcttggtctc cagcggttga ggctggaagc accggggtgc ggtggaaagg 420

gctctgtcca ggaagaccgg atccgcagag ccgggagtcc gggctaggaa gtccctttct 480

cggtgggaga ctgaggccgc cttggcgggg cgggacgaga ctcctccgag gtcgggaaag 540

ggggccccgc agcagcccct tggcttccct tctcccttgc ctcccctccg gggctccggt 600

tcagaggcac tctgggcgcc tgctacagct tccaaactgc gccgcttcct tcttcggcag 660

aaaaggactt tcagatgcgg cggcggcggc ggcggcgact caggacagcg ccccctcccc 720

taacggccgc ctctccctct cccctcgcc cgccccggct cccccacctc tgggaaggcg 780

ctgggggtgt ggccagggac cggtataaag tccgggggag ccggtcccgg gcagccgctc 840

agccccctgc ccctcgccgc ccgccgcctg cctgggccgg gccgaggatg cggcgcagcg 900

cctcggcggc caggcttgct ccctccggca cgcctgctaa cttcccccgc tacgtccccg 960

ttcgcccgcc gggccgcccc gtctccccgc gccctccggg tcgggtcctc caggagcgcc 1020

aggcgctgcc gccgtgtgcc ct 1042

<210> 139
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 139
tcgtcgtttt gacgttttgt cgtt 24

<210> 140
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 140
tcgtcgtttt gtcgtttttt tcga 24

<210> 141
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 141
tcgtcgtttc gtcgtttcgt cgtt 24

<210> 142
<211> 24
<212> DNA
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<220>
<223> Immunostimulatory nucleic acid

<400> 142
tcgtcgtttc gtcgttttgt cgtt 24

<210> 143
<211> 21
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 143
tcgtcgtttt tcggtcgttt t 21

<210> 144
<211> 22
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 144
tcgtcgtttt tcgtgcgttt tt 22

<210> 145
<211> 22
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 145
tcgtcgtttt cggcggccgc cg 22

<210> 146
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 146
tcgtcgtttt acggcgccgt gccg 24

<210> 147
<211> 24
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<213> artificial sequence
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<223> Immunostimulatory nucleic acid

<220>
<221> misc_feature
<222> (2)..(2)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (5)..(5)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (13)..(13)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (21)..(21)
<223> N = 5-methylcytosine

<400> 147
tngtngtttt gtngttttgt ngtt 24

<210> 148
<211> 27
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<220>
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<222> (2)..(2)
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<220>
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<222> (5)..(5)
<223> N = 5-methylcytosine

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<221> misc_feature
<222> (7)..(7)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (11)..(11)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (13)..(14)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (16)..(16)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (19)..(19)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (22)..(22)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (26)..(27)
<223> N = 5-methylcytosine

<400> 148
tngtngntgt ntnngnttnt tnttgnn 27

<210> 149
<211> 21
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<220>
<221> misc_feature
<222> (2)..(2)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (8)..(8)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (10)..(10)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (13)..(13)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (16)..(16)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (20)..(20)

<223> N = 5-methylcytosine
<400> 149 21
gngtttgntn ttnttnttgn g

<210> 150
<211> 20
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<220>
<221> misc_feature
<222> (2)..(4)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (8)..(8)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (12)..(12)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (15)..(16)
<223> N = 5-methylcytosine

<220>
<221> misc_feature
<222> (19)..(19)
<223> N = 5-methylcytosine

<400> 150 20
gnnnaagntg gnatnngtna

<210> 151
<211> 15
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 151 15
tcctggcggg gaagt

<210> 152
<211> 42
<212> DNA
<213> artificial sequence

<220>

<400> 152
gaaactcgag ccaccatgag acagactttg ccttgtatct ac 42

<210> 153
<211> 37
<212> DNA
<213> artificial sequence

<220>

<223> Oligonucleotide

<400> 153
gaaagaattc ttaatgtaca gagtttttgg atccaag 37

<210> 154
<211> 24
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 154
tgctgctttt gtgcttttgt gctt 24

<210> 155
<211> 20
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 155
tccatgacgt tcctgatgct 20

<210> 156
<211> 20
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 156
tccatgagct tcctgatgct 20

<210> 157
<211> 20
<212> DNA
<213> artificial sequence

<223> Immunostimulatory nucleic acid

<220>
<221> misc_feature
<222> (8)..(8)
<223> N = 5-methylcytosine

<400> 157
tccatgangt tcctgatgct 20

<210> 158
<211> 22
<212> DNA
<213> artificial sequence

<220>

<223> Immunostimulatory nucleic acid

<400> 158
tcgtcgtttt cggcgcgcgc cg 22

<210> 159
<211> 21
<212> DNA
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